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VOLUME 34

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CONTENTS OF VOLUME 34

JULY, 1927. NUMBER 1 PAGE

The Influence of Pathology on the Development of Pediatrics. Isaac A. Abt, M.D., Chicago 1

Respiratory Anaphylaxis: Sensitization, Shock, Bronchial Asthma and Death Induced in the Guinea-Pig by the Nasal Inhalation of Dry Horse Dander. Bret Ratner, M.D.; Holmes C. Jackson, Ph.D., and Helen Lee Gruehl, B.A., New York 23

The Relation of Maternal Diet to Hemorrhage in the New-Born. C. Ulysses Moore, M.D., and Jesse Laird Brodie, M.A., Portland, Ore 53

Malignant Neuroblastoma: Report of Three Cases. Boris Kwartin, M.D., and J. Russell Twiss, M.D., New York 61

Sickle Cell Anemia: Report of a Case with Splenectomy. Walter Blair Stewart, M.D., Atlantic City, N. J 72

Dermatoses Due to Light Sensitization, with Special Reference to the Cutaneous Dangers of Ultraviolet Radiation in Children. Sigmund S. Greenbaum, M.D., Philadelphia 81

Progress in Pediatrics:
Child Health in the Past. Philip Van Ingen, M.D., New York 95

News and Comment 103

Obituary:
Abraham Zingher, M.D 105

Abstracts from Current Literature 106

Society Transactions:
Pediatric Section of the Academy of Medicine of Cleveland 131
American Pediatric Society (first and second sessions) 133

Book Reviews 154

Directory of Pediatric Societies 155

AUGUST, 1927. NUMBER 2

Effect of Therapeutic Doses of Ultraviolet Radiation on Basal Metabolism in Children.
First Paper. Margaret E. Fries, M.D., New York 159
Second Paper: Immediate Effect. Margaret E. Fries, M.D., and Anne Topper, M.D., New York 166

Enlargement of the Spleen in Children. Adrien Bleyer, M.D., St. Louis 176

Pyloric Stenosis of Infants. F. F. Tisdall, M.D. (Tor.); M. W. Poole, M.D., and Alan Brown, M.B. (Tor.), Toronto 180

Inorganic Blood Phosphate: Studies of Rats on Rachitic and Nonrachitic Diets. Elizabeth M. Koch, Ph.D., and Meyer H. Cahan, M.S., Chicago 187

Papilledema and the Diagnosis of Epidemic Encephalitis. Lester Rosenberg, M.D., New York 198

Hiccups Among Infants. Walter R. Pendleton, S.B., Long Beach, Calif 207

Studies in Pubescent Growth, with Special Reference to Periodic Gain. Borden S. Veeder, M.D., and E. H. Rohlfing, M.D., St. Louis 211

Metabolism of Salts in Nephritis: III. Chlorides and Sodium. Gladys L. Boyd, M.D. (Tor.); Angelia M. Courtney, B.A., and Ida F. MacLachlan, B.A., Toronto 218

Renal Infantilism: Report of a Case and a Review of the Literature. F. C. Hunt, M.D., New York 234

Chronic Intussusception: An Unusual Type with Prolapse. Oscar B. Markey, M.D., Cleveland, and Katsuji Kato, M.D., Los Angeles 249

Progress in Pediatrics:
Diphtheria in Infancy. S. F. Ravenel, M.D., Greensboro, N. C 258

AUGUST, 1927—Continued

PAGE
Abstracts from Current Literature 263
Society Transactions:
American Pediatric Society (Third and Fourth Sessions) 302
Book Reviews 321
Directory of Pediatric Societies 323

SEPTEMBER, 1927. NUMBER 3

Mikulicz's Syndrome: A Report of Ten Cases. Alexander J. Schaffer, M.D., and A. Wilmot Jacobsen, M.D., Baltimore 327
Anemia in Children, with Splenomegaly and Peculiar Changes in the Bones: Report of Cases. Thomas B. Cooley, M.D.; E. R. Witwer, M.D., and Pearl Lee, M.D., Detroit 347
Antirachitic Properties of Irradiated Dry Milk. G. C. Supplee, Ph.D., and Odessa D. Dow, M.S., Bainbridge, N. Y. 364
Cirrhosis of the Pancreas and Liver in an Infant. Cornelia De Lange, M.D., Amsterdam, The Netherlands 372
Talipomanus: A Report of Three Cases in One Family. Edgar E. Martmer, M.D., Detroit 384
Rickets: An Unusual Roentgenographic Manifestation. Philip Lewin, M.D., Chicago 388
The Heart and Blood Vessels in Congenital Syphilis. Irving Matusoff, M.D., and Paul D. White, M.D., Boston 390
Microprecipitation Test for Syphilis. M. G. Peterman, M.D., Milwaukee .. 404
Prevention and Treatment of Thrush (Oidial Stomatitis). Harold K. Faber, M.D., and Esther B. Clark, M.D., San Francisco 408
Etiology of Respiratory Disease in the City and Country School of New York City. Edith M. Lincoln, M.D., New York 418
Chvostek's Facialis Sign in New-Born Infants. Frank E. Stevenson, M.D.; A. Graeme Mitchell, M.D., and Carl A. Koch, M.A., Cincinnati 425
Gastric Digestion: The Relation of the Hydrogen Ion Concentration Volume and Buffer Capacity of the Gastric Contents to a Milk Test Meal. Raymond B. Miles, M.D., Brooklyn, and Alfred T. Shohl, M.D., New Haven, Conn 429
Mushroom Poisoning Due to Hebeloma Crustuliniforme: Report of Four Cases. H. W. Price, M.D., Baltimore 441
Progress in Pediatrics:
Evidence of Rickets Prior to 1650. John A. Foote, M.D., Washington, D. C. 443
News and Comment 453
Abstracts from Current Literature 456
Society Transactions:
American Child Health Association 501
Chicago Pediatric Society 513
St. Louis Pediatric Society 515
Book Reviews 518
Directory of Pediatric Societies 521

OCTOBER, 1927. NUMBER 4

Bacteriophage and Skin Tests in Diarrhea of Unestablished Etiology in Children. Carl Krenz, M.D., Cleveland 525
Prophylaxis of Varicella with Vesicle Fluid. William W. Waddell, Jr., M.D., and R. Cannon Eley, M.D., University, Va 540
Dientamoeba Fragilis. John C. Gittings, M.D., and Arthur D. Waltz, M.D., Philadelphia 542
Pulmonary Tuberculosis in Infants: Bacteriologic Diagnosis by Examination of the Stomach Contents. P. F. Armand-Delille, M.D., Paris, France 547
Nondiabetic Ketosis in Children. Charles A. Weymuller, M.D., and Oscar M. Schloss, M.D., New York 549
Premature Infants: A Report of Two Hundred and Sixty-Six Consecutive Cases. Julius H. Hess, M.D., and I. McKy Chamberlain, M.D., Chicago 571

OCTOBER, 1927—Continued

PAGE

The Early Occurrence of Gastric Hemorrhage in Children with Splenomegaly. Richard M. Smith, M.D., and Philip J. Howard, M.D., Boston 585
Acute Phosphorus Poisoning: Report of a Case with Recovery. Rustin McIntosh, M.D., New York 595
Ureteral Stricture and Chronic Pyelitis in Children. Guy L. Hunner, M.D., Baltimore 603
The Treatment of Persistent Rickets. Max W. Bloomberg, M.D., Montreal 624
Diaphragmatic Paralysis Resulting from Injury of the Brachial Plexus. J. W. Epstein, M.D., Cleveland 634
Intussusception Terminating in "Spontaneous Elimination": Report of a Case with Complete Recovery. Lawrence D. Thompson, M.D., St. Louis 640
Progress in Pediatrics:
Persistent Vaginal Discharge in Infants and in Little Girls: Cause and Treatment. Goodrich C. Schauffler, M.D., Portland, Ore 644
News and Comment:
Preliminary Report from Institutions for Feebleminded and Epileptic Patients in Thirty-Six States 657
Meeting of Congress International de l'Enfance 657
Abstracts from Current Literature 658
Society Transactions:
Canadian Society for the Study of Diseases of Children 697
Chicago Pediatric Society 703
Book Reviews 713
Directory of Pediatric Societies 715

NOVEMBER, 1927. NUMBER 5

Ultraviolet Radiations: Measurement by the Acetone Methylene Blue Method. C. H. Best, M.D., and J. H. Ridout, M.A., Toronto 719
Seasonal Variation of the Antirachitic Effect of Sunshine. Frederick F. Tisdall, M.D. (Tor.), and Alan Brown, M.B. (Tor.), Toronto 721
Antirachitic Effect of Skyshine. Frederick F. Tisdall, M.D. (Tor.), and Alan Brown, M.B. (Tor.), Toronto 737
Antirachitic Value of the Sun's Rays Through Various Special Window Glasses. Frederick F. Tisdall, M.D. (Tor.), and Alan Brown, M.B. (Tor.), Toronto 742
Does the Irradiation of Cod Liver Oil Increase Its Antirachitic Potency? Edwin T. Wyman, M.D.; Arthur D. Holmes, Ph.D.; Lawrence W. Smith, M.D.; Donald C. Stockbarger, Sc.D., and Madeleine G. Pigott, B.S., Boston 753
The Epiphyseal Changes in the Diagnosis of Scurvy. A. B. Schwartz, M.D., Milwaukee 765
Generalized Edema of Undetermined Etiology: Report of an Unusual Case. William L. Rost, M.D., New York 773
Phlyctenular Keratoconjunctivitis: Its Etiology and Treatment. Horton Casparis, M.D., Nashville, Tenn 779
Nontuberculous Fibrosis of the Lungs. H. Harris Perlman, M.D., Ph.D., Philadelphia 787
Isolated Lymphoid Hyperplasia in the Cecum and Appendix of Children. A. P. Stout, M.D., New York 797
Physiologic Variations in the Leukocytes in Infants and in Children. E. Gordon Fletcher, M.D., and A. Graeme Mitchell, M.D., Cincinnati 807
Asthma in Children: VI. A Comparative Study of the Scratch and Intradermal Methods of Skin Testing. M. Murray Peshkin, M.D., and A. H. Fineman, M.D., New York 815
Parathyroid Therapy in Infantile Tetany: Report of Four Cases. A. H. Gibson, M.D., Elkhart, Ind 835
Scarlet Fever: IV. Amato Bodies in Scarlet Fever. John A. Toomey, M.D., and John A. Gammel, M.D., Cleveland 841
A Study of the Antirachitic Factor in Human and in Cow's Milk. Alfred F. Hess, M.D., and Mildred Weinstock, B.S., New York 845
The Spleen in Measles. Emanuel Friedman, M.D., Denver 854
Spontaneous and Induced Ketosis in Children: Effect on the Glucose Tolerance Test. Jerome L. Kohn, M.D.; Margaret E. Fries, M.D., and Gertrude Felshin, M.D., New York 857

NOVEMBER, 1927—Continued PAGE

Feeding Care of the Infant in the Obstetric Nursery. Frank C. Neff, M.D., Kansas City, Mo. 870
Progress in Pediatrics:
The Technic of Teaching. John Lovett Morse, M.D., Boston. 877
News and Comment. 883
Abstracts from Current Literature. 884
Society Transactions:
Association of American Teachers of the Diseases of Children. 914
Book Reviews. 918
Directory of Pediatric Societies. 919

DECEMBER, 1927. NUMBER 6

Sickle Cell Anemia: Reports of Two Cases in Young Children in Whom Splenectomy was Performed. Albert J. Bell, M.D.; Robert H. Kotte, M.D., and A. Graeme Mitchell, M.D., Cincinnati, and Thomas B. Cooley, M.D., and Pearl Lee, M.D., Detroit. 923
Celiac Disease (Chronic Intestinal Indigestion): Etiology, Prognosis and Standardization of Treatment. Louis W. Sauer, M.D., Evanston, Ill.. 934
The Intradermal Saline Test in Serum Sickness. William L. Bradford, M.D., Rochester, N. Y. 950
Rickets in the Negro: Effect of Treatment with Ultraviolet Rays. Sandor A. Levinsohn, M.D., Paterson, N. J. 955
Tuberculosis of the Cervical Lymph Nodes in Infancy: Value of the Roentgen Ray in Diagnosis. Ethel C. Dunham, M.D., and Arnold M. Smythe, M.D., New Haven, Conn. 962
Congenital Heart Block: Report of a Case. Rustin McIntosh, M.D., New York. 965
Scarlet Fever: I. The Relation Between Antitoxin in the Blood and Skin Sensitivity to Toxin in New-Born Infants and in Their Mothers. Jean V. Cooke, M.D., with the Technical Assistance of Hazel R. Keith, A.B., and Lucille Ermatinger, A.M., St. Louis. 969
Fever in the New-Born. Ralph M. Tyson, M.D., Philadelphia. 979
The Icterus Index in Children. Rood Taylor, M.D., Minneapolis. 989
Seasonal Variation in the Calcium Content of Infants' Serum. Harry Bakwin, M.D., and Ruth Morris Bakwin, M.D., New York. 994
The Estimation of Renal Efficiency of Children: Studies on the Excretion of Nitrogen. I. M. Rabinowitch, M.D., C.M., and R. Breitman, M.D., C.M., Montreal, Canada. 1000
Blood and Cerebrospinal Fluid Sugar. Harold G. Grayzel, M.D., and Elsa R. Orent, B.S., Brooklyn. 1007
Epilepsy in Children: Relationship of Variations in the Degree of Ketonuria to Occurrence of Convulsions in Epileptic Children on Ketogenic Diets. Irvine McQuarrie, Ph.D., M.D., and Haddow M. Keith, M.B. (Tor.), Rochester, N. Y. 1013
Erysipelas: A Clinical Study of the Treatment of This Disease. E. S. Platou, M.D.; F. W. Schlutz, M.D., and Loren Collins, M.D., Minneapolis. 1030
The Bacteriology of Dried Powdered Milk Preparations Used in Infant Feeding. George F. Dick, M.D., and Gladys Henry Dick, M.D., Chicago. 1040
Tuberculin Tests in Children: A Comparative Study of Human and Bovine Tuberculin. Adolph G. DeSanctis, M.D., New York, and Henry A. Reisman, M.D., Jamaica, L. I. 1042
Progress in Pediatrics:
Congenital Atresia of the Colon. Norris J. Heckel, M.D., and C. W. Apfelbach, M.D., Chicago. 1050
News and Comment:
American Medical Association of Berlin. 1056
Abstracts from Current Literature. 1057
Society Transactions:
Chicago Pediatric Society. 1086
Book Reviews. 1100
Directory of Pediatric Societies. 1103
General Index. 1107

...ical

JUL 28 1927

VOLUME 34 NUMBER 1

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CONTENTS OF PREVIOUS NUMBER

JUNE, 1927. NUMBER 6

Growth of the Thymus: Its Relation to Status Thymicolymphaticus and Thymic Symptoms. Edith Boyd, M.D., Minneapolis.

Asthma in Children: III. The Incidence and Significance of Various Diseases and Infections, and of Tonsillectomy and Adenoidectomy. M. Murray Peshkin, M.D., New York.

Bacteremia in Diphtheria: Invasion of the Blood Stream by the Klebs-Loeffler Bacillus and Associated Organisms. Edgar Martmer, M.D., Detroit.

Essential Thrombocytopenia: Report of a Case in an Infant Aged Four Months. Harry M. Greenwald, M.D., Brooklyn.

Effect of Potent Parathyroid Extract on Calcium Balance in Infants. Lynne A. Hoag, M.D.; Helen Rivkin, M.A.; Carl E. Weigele, M.D., and Frieda Berliner, A.B., New York.

Anuria of Seven Days' Duration in a Child with Scarlet Fever. Harold L. Higgins, M.D., and William J. Graf, M.D., Cincinnati.

Gonococcus Arthritis in Infancy: A Clinical Study of Forty-Four Cases. Morris B. Cooperman, M.D., Philadelphia.

Syphilitic Cirrhosis of the Liver in an Infant. V. Joukovsky, M.D., Smolensk, Russia.

Sanguineous Lacrimation: Report of a Case. Z. R. Scott, M.D., Pittsburgh.

Volvulus: Report of a Case in an Infant Aged Fifteen Days. James W. Bruce, M.D., Louisville.

Progress in Pediatrics:

Urologic Problems in Infancy and Childhood. Herman L. Kretschmer, M.D., Chicago.

News and Comment.

Obituary:

Henry Koplik, M.D.

Abstracts from Current Literature.

Society Transactions:

Chicago Pediatric Society.
Northwestern Pediatric Society.

Book Reviews.

Directory of Pediatric Societies.

General Index.

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American Journal of Diseases of Children

VOLUME 34 JULY, 1927 NUMBER 1

THE INFLUENCE OF PATHOLOGY ON THE DEVELOPMENT OF PEDIATRICS*

ISAAC A. ABT, M.D.
CHICAGO

The origin of pathologic anatomy may be traced to the earliest human record. The ancient Egyptians and Greeks had at least a slight conception of this subject. Pliny states that the kings of Egypt ordered the bodies of the dead opened so that physicians might find the diseases responsible for death. The writings of Aristotle and Hippocrates contain several passages which show that in their time human bodies were dissected. When the scepter of supremacy in medicine passed from the Greeks to the Arabians, dissection received but scant attention. The ancients, whether one refers to the illustrious East Indian or Arabian physicians, to Hippocrates himself or to Galen, had little if any conception of morbid changes in the body; but occasionally some historian has detected a flash of wisdom about pathology in their writings.

Hippocrates recognized caput succedaneum and cephalhematoma. He described congenital malformations such as dislocations of the hip and clubfeet. He must have been acquainted with diphtheria, for he described a form of membranous pharyngitis which produced exudation over the tonsils, and compared it in appearance to a spider web. If this exudation was forcibly removed, it would recur. He observed that impaired deglutition sometimes occurred as a sequel of this disease.

Hippocrates was interested in morbid anatomy, as attested by his statement of surprise that those physicians who attended the Emperor Marcus Aurelius in his campaign against the Germans had the opportunity of dissecting the bodies of the barbarians slain in battle, but failed to make use of it.

In the writings of Galen, who lived about 131 A.D., are references to child hygiene and some general observations on clinical conditions. He mentions congenital atresia of the urethra, hydrocele, hermaphroditism, hydrocephalus and exomphalos. He gives an account of a condition that historians believe was infantile rickets.

Soranus of Ephesus (98-117 A.D.) was a historian of Hippocrates. He was distinguished for his obstetric and gynecologic knowledge, and

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his ideas on these subjects prevailed until recent times. Soranus, like his successors, treated the diseases of infancy, and gives the most remarkable and complete account of pediatrics in antiquity. He was an independent thinker and made numerous observations concerning the hygiene and treatment of the infant. He discussed skin diseases, brain fever and diarrhea, and commented on the frequency of crooked limbs in Roman children. From latter reference it has been thought that he recognized clinical rickets.

Among the masters of ancient medicine, one could undoubtedly find many treasures of knowledge and wisdom referring to morbid anatomy. It is not my purpose, however, to render a long dissertation on the pediatric achievements or failures of ancient medicine. I wish to trace, as briefly as possible, the influence of pathology on the development of pediatrics. The Middle Ages present little or nothing of interest to the historian who attempts to develop the subject from this standpoint. This period, when men were more concerned with their souls than with their bodies, was barren of productive scientific effort.

In the pride of present knowledge, however, physicians should not turn with contempt on the follies of their predecessors. They were seekers after truth, but they fell into error and failed. They frequently philosophized without constructing logical or fundamental deductions on the basis of facts. Medicine was dominated during the dark ages by the alchemists, astrologers, necromancers and sorcerers—those who pretended to discover futurity as well as those who dealt in charms, amulets and universal panaceas, and who compounded synthetic powders. They were a motley group of quacks, empirics and charlatans.

The healing art was subservient to the religious spirit of the age, and the literary efforts consisted of rewriting and interpreting the works of the ancient masters, and maintaining their historic values. Even Paracelsus (1493-1541), after he had achieved great success as a practitioner at Basle, forsook his native city after a disagreeable experience with a patient about the payment of a fee. He became a wanderer through Europe, supporting himself, as he traveled, on the credulity and infatuation of all classes of society. In spite of his astrologic inclinations, history accords him an important place as a master-mind of his period. Paracelsus was a capable physician, and his real services were acknowledged by his successors who organized a sect to perpetuate his doctrines. He advocated chemical therapeutics, and made opium, mercury and other drugs a part of the pharmacopeia. He distinguished alum from ferrous sulphate and popularized tinctures and alcoholic extracts.

His pathologic knowledge was of considerable extent, in spite of his views on astrology. He considered gout and nephrolithiasis a diathesis caused by precipitation of substances ordinarily voided from the body. The coincidence of cretinism and epidemic goiter was first noted by him.

With the Renaissance, natural philosophy was introduced. Paracelsus incorporated this form of knowledge in his teaching. It was Paracelsus who shook the widespread teaching of Galen. While there remained many who still believed in the Galenic biology and pathology, nevertheless the introduction of chemical and biologic factors into the etiology of disease, as well as the introduction of chemical drugs, marked the beginning of a new era in medical thought.

In almost every branch of science new ideas were forming at this time, and another kind of man was interested in science. Galileo, the founder of mechanics, suggested a new method of thinking. Questions were now being put. What are the fundamental causes for this or that phenomenon? Galileo introduced scientific procedures and believed that things should be demonstrated experimentally.

With the beginning of this period, the worship of the ancient philosophers waned. The teachings of Aristotle and Galen became less authoritative. Bacon founded inductive philosophy, and Descartes elucidated the principles of scientific method. The spirit of scientific inquiry and clarified intellectual atmosphere dominated the thought prevalent at this time.

This introduction of the scientific method had a definite influence on the trend of medical thought; as a result, morbid anatomy eventually became the foundation on which clinical medicine was based. A most important contribution to the development of the new science was the discovery of the circulation of the blood by William Harvey (1578-1657).

Harvey's discovery, 1628, should not be considered exclusively the result of the anatomic reforms of Vesalius. The new thought of Harvey expresses the spirit, thought and method of the recent school of natural philosophy. Harvey's discovery was the result of an experimental study on the heart and the valves of veins, carried on by vivisections on cold-blooded animals and higher mammals. He failed to recognize the capillaries which were discovered by Malpighi. At a later date Malpighi described the complete circulation, which abolished entirely the old blood division theory of Galen.

Harvey's discovery at first encountered great opposition, as did the publications of Vesalius; but gradually these teachings prevailed and were accepted. It was possible for a group of anatomic and physiologic studies to follow, so that both anatomy and physiology grew into important and dignified positions. Somewhat later, the magnifying glass was discovered by Leuwenhoeck, who recognized the importance of magnification and microscopy for medicine.

Francis Glisson (1597-1677), a pupil of Harvey, was a professor at Cambridge and later a practitioner in London. Although he was an

anatomist, pediatricians are especially interested in him because of his original investigations on rickets.

Some valuable researches on the relationship of the lymphatics to the intestines were made by Glisson, and his anatomic studies on the liver are of classic importance. He described the irritability of muscles, which was confirmed and placed on an experimental foundation by Haller in the eighteenth century. Glisson employed a speculative process, by which he saw a vital property of the entire organism which he called "irritability".

It was soon to be recognized that pathologic anatomy was fundamental to the knowledge of disease. Vesalius (1514-1564), the first of the anatomists, whose studies were for the most part of the descriptive type, took pains in the observation of abnormalities. He was probably the first to describe, anatomically, internal aneurysm. The statement is attributed to him, "I am very sorry not to have devoted to pathological anatomy the large amount of time and strength which I spent on normal anatomy".

In the last of the fifteenth century, Antonio Benivieni, a practitioner and medical scholar, recorded his life experiences, which were published in 1507, five years after his death. Aside from the usual clinical reports, he records 111 autopsies containing descriptions of a variety of disorders. It was unusual, during this period, for a physician to be interested in morbid anatomy.

Sydenham (1624-1684) was not interested in the study of the dead body, as such investigations made no appeal to him.

In the seventeenth century, the clinical nature of diseases was studied by methods of observation, and various systems of disease were proposed. Monographs and epidemiologic treatises such as those of Sydenham were being published. Here and there pathologic studies were being pursued. Theophile Bonet (1620-1689), a Swiss physician of Geneva, published, in 1679, "Sepulchretum Anatomicum". In the two large volumes all the pathologic and anatomic data of the sixteenth and seventeenth centuries were collected. In addition, many hitherto undescribed conditions were compiled from the meager literature. Bonet has been called the predecessor of Morgagni in pathologic anatomy. Boerhaave held Bonet in high regard and recommended him as a teacher and master who was fit to confer a degree.

Herman Boerhaave (1668-1738) was a lecturer on medicine and botany and professor of chemistry at the University of Leyden. This man occupies an important position in the evolution of the subject, because he did much to advance the cause of science in the eighteenth century. He was one of the first to organize systematic clinical teaching. After instructing in botany and chemistry, he became professor of physics. His publications are best known through his aphorisms which influenced the

practice of medicine during the eighteenth century. Physicians' greatest debt to him is for his gift of two eminent scholars, his former students, Gerhard van Swieten (1700-1772) and Albrecht von Haller (1708-1777).

Auenbrugger of Vienna in 1761 described direct percussion in order to demonstrate hypertrophy of the heart. Corvisart gracefully gave full credit to Auenbrugger for the discovery of percussion. He wrote, "It is he (Auenbrugger) and the beautiful invention which of right belongs to him that I wish to call to life." It will be recalled that Auenbrugger was a student of Baron van Swieten, who in turn had been a pupil of Boerhaave.

One cannot conceive of the origin of morbid anatomy without thinking at once of John Baptist Morgagni (1682-1772). At times one is unmindful of the debt owed to those pioneers who laid the foundations of knowledge on which modern theory and practice are based. From the beginning of the Renaissance to the present, there have been, at varying periods, men who blazed the way and made investigations which caused the rejection of old traditions and beliefs and which heralded new truths. Such a man was Morgagni.

His fame arises from the variety and excellence of his labors, and to him belongs the credit for establishing morbid anatomy as the basis for the diagnosis and rational treatment of disease.

Originally, he devoted himself to descriptive anatomy. The inspiration of Morgagni came to him as a hereditary right from his teachers. He was an intimate friend and student of Valsalva, and Valsalva had studied under Malpighi. Morgagni learned the art of teaching from Valsalva, and in his writings he frequently refers to his master with the greatest reverence.

Morgagni will be remembered for all time by the publication of the volume, "The Seats and Causes of Diseases," published in 1761. The author was at this time in his eightieth year. This might be taken as a valuable guide to modern writers. It is a part of wisdom to write at the close of one's career, so that one may record his life's experiences reflectively, and avoid the mistakes and follies of his youth. The publication of this work marked a new epoch in medicine. Up to this period the anatomy of diseased organs had not been described systematically. What Vesalius was to normal anatomy, Morgagni was to morbid anatomy.

He performed autopsies on children and recorded his observations. Congenital heart disease, with hypertrophy and dilatation of the right ventricle, open foramen ovale and stenosis of the pulmonary valves were described by him. He also described a case of tuberculosis in a child, and prolapse of the urethra in a female infant. He lamented the fact

that, owing to the tenderness of mothers, postmortem examination of children was only occasionally permitted.

The fame of Albrecht von Haller (1708-1777) is so well established that he should not be omitted from the illustrious group who shaped the fortunes of medical progress. He is regarded as one of the most acute medical intellects of the eighteenth century, equally eminent as anatomist, physiologist and botanist. He was a student of Boerhaave, Albinus and Winslow.

The experiments of Glisson were repeated by him, and he showed the excitability and contractility of muscle tissue. He published a book on the physiology of the human body which remained a classic and entitled him to the position of founder of physiology.

While a tendency exists, especially in these later days, to separate the specialties, modern clinical medicine could not have risen to its present position unless all of the fundamental medical sciences had taught us the lessons of structure, function and dysfunction. Anatomy, physiology, pathology and chemistry are of equal importance in the evolution of medicine. Physicians should not be overzealous in stressing one to the exclusion of another.

Shortly after the revival of medicine under Morgagni in Italy, William and John Hunter and their students introduced a new era of anatomy, morbid anatomy and surgery in the British Isles. Matthew Baillie (1761-1823) was the nephew of John and William Hunter. Baillie's principal published work consists of pathologic treatises. In 1793 appeared his work, "The Morbid Anatomy of Some of the Most Important Parts of the Human Body." It met with great success and was translated into many European languages. He described endocarditis, gastric ulcer and ulceration of Peyer's patches in typhoid fever. Rheumatism of the heart was mentioned. He gave the first accurate description of hepatization of the lung in pneumonia. For his inspiration as a pathologist he was greatly indebted to his uncles, William and John Hunter.

But shortly, medicine moved its temple to France to come under the leadership of Francois Xavier Bichat (1771-1802). Bichat is usually, and with justice, mentioned as the man who set up the landmark between the two centuries in medicine. In his twenty-first year he gave his first course in anatomy. At the same period, he was devoting much of his time and attention to experimental physiology. In addition, he was assisting his master, Desault, in the practice of surgery.

He published his researches on "The Nature and Function of Serous Membranes," which was an important paper in physiologic investigation. The literature of medicine was also enriched with his original observations on synovial membranes and the symmetry of different organs. Finally, he classified diseases, and in order to discover their nature and

their location, he made a vast number of autopsies. With these studies as a basis, he delivered a course of lectures on pathologic anatomy.

He was inspired by the work of his predecessor, Philippe Pinel (1756-1826), who attempted to determine diagnosis on the basis of carefully considered symptoms. Another idea of his was that definite tissues and organs became diseased and these diseases he attempted to differentiate. Undoubtedly, he was influenced by the artificial classifications of Linnaeus and others who were making botanic studies.

Bichat died at the early age of 31, and left an indelible impression on the medical thought and progress of all time. The French school of clinicians were stimulated by his work. Bichat spent his whole day in the dissecting room of the Hotel Dieu, and Corvisart was one of his eager students who was studying pathologic anatomy, so that he might perfect his knowledge of clinical medicine. Bayle and Laennec were also his pupils.

At the beginning of the nineteenth century there were two clinical schools in Paris. Philippe Pinel conducted his course at the Salpêtrière and attracted the larger number of students. His discussions were theoretical, and he attempted to classify diseases.

Jean Nicholas Corvisart (1755-1821) presided over the clinic at La Charité. His teachings were based on morbid anatomy, and he was a clinician in the more modern sense of the word. As one would say today, he specialized on the heart, and he was among the first who studied disease in a special organ. In his cardiac studies he practiced percussion and auscultation, and he described the thrill accompanying mitral stenosis. He reintroduced the teachings of Auenbrugger on percussion, which had been practically neglected since the latter presented them in 1761.

Corvisart's greatest contribution to medicine was this revival of immediate percussion. He followed his clinical cases to the autopsy table, a practice which was of great value to him and to others in advancing the knowledge of clinical diagnosis and internal medicine. He may be classed among the first and ablest of the clinicians and diagnosticians of this period and deserves to be ranked as the father of modern diagnosis.

Rene Theophile Hyacinthe Laennec (1781-1826) attached himself to the school of Corvisart. It may be truly said of him that he was a clinician of the highest rank. Originally, he devoted himself to morbid anatomy, and distinguished himself in the description of tissues found postmortem. He contributed much to the knowledge of pathology, by classifying his observations and correlating the symptoms present during life with the appearances of tissues after death.

Many of his studies refer to conditions that were unknown before his time, or at least, if they were known, were not properly understood.

Among these may be mentioned: pulmonary tuberculosis, pneumonia, pulmonary apoplexy, edema, gangrene and emphysema, dilatation of the bronchial tubes, hydrothorax, pneumothorax and some forms of cardiac disease.

He was one of the founders of the clinical-morbid anatomy method of studying disease, which still remains the cornerstone of medicine.

In 1819, Laennec announced his discovery of auscultation with the stethoscope, which marked the beginning of physical diagnosis. He described râles, rhonchi, crepitation, heart sounds and murmurs, and in addition to all this, he interpreted these sounds and told definitely what they signified. His book, "De l'Auscultation Mediate," published in 1819, contained the results of his investigations and will always remain a classic in medical literature.

His clinical and pathologic descriptions of tuberculosis constitute perhaps the most masterly chapter in clinical medicine. He described the respiratory sounds in children, and says, "The difference in these sounds from those of the adult is chiefly noted during inspiration." He was of the opinion that the difference proved that children require a larger amount of air than adults, and that consequently inspiration is more complete with them.

After Corvisart, his pupils and successors, Bayle, Andral, Bouillaud, Chanel, Piorry, Bretonneau, Rayer, Cruveilhier and Trousseau, brought a new spirit into medicine. Pierre Bretonneau (1771-1862) was a distinguished physician of this period. He is best remembered by his contributions to the knowledge of diphtheria and typhoid fever. Tracheotomy for the relief of laryngeal stenosis was first performed by him. He was the teacher of Trousseau. In the introduction of his "Memoirs on Diphtheria," he writes, "It is the opinion of Laennec that diseases cannot be more certainly distinguished than by their anatomical characters. Deeply imbued with this opinion, I have never neglected any occasion of multiplying my necroscopic researches during the course of the epidemic which I have been called upon to observe. It is only, in fact, by following the changing aspect of every morbid lesion and by comparing the results of a great number of observations made at different times and places that it is possible to determine the alterations which belong to one and the same disease."

It may be said that the scientific history of diphtheria began with Bretonneau, since he was the first to write diphtherial angina and croup into an etiologic and clinical entity.

Pierre Charles Alexandre Louis (1787-1872) was the logical successor of Laennec and the exponent of exact clinical methods. He opposed the arbitrary doctrines of Broussais, and succeeded in overthrowing the fantastic theories of the latter. He taught the value of

accurate clinical observations and used extensively the method of statistics in evaluating the importance of symptoms and disease manifestations.

In this way he proved that phlebotomy was excessively performed in the treatment of pneumonia. His essay on phthisis was based on postmortem and clinical observations, and his treatise on typhoid fever revealed the differential diagnosis between this disease and typhus. In doing this, he cleared up one of the most obscure problems of his time. Students from all countries flocked to his clinic to be inspired by his instruction.

W. W. Gerhard of Philadelphia interpreted his teachings on typhoid fever. Oliver Wendell Holmes, who was a student of Louis, tells in his "Medical Essays" that he held Louis in great reverence and considered him the greatest teacher who ever was or ever would be. He said that the young men of his day hardly knew how much they were indebted to this great master. Holmes characterized Louis' treatise against bleeding in pneumonia as the greatest contribution since the days of Sydenham.

Bichat and Laennec of the French school stimulated students of pathology and internal medicine to investigation and study. Before their time, the diseases of young-life had received only cursory attention from this new school of thinkers. It remained for Charles-Michel Billard (1800-1832) to systematize and organize the knowledge of pediatrics and correlate the clinical data with morbid anatomy. In 1828 he published his treatise on the diseases of new-born infants and nurslings.

In the preface to the first edition Billard says that one day, while reading Morgagni, a favorite author, he was particularly struck by the statement, "How vast and new is the space that is still open before us for the study of the diseases of young children." From Morgagni's day, Billard continues, many men have attempted to extend the boundaries of science, and he desires to glean the facts that have escaped the notice of his predecessors and to add some recently ascertained truths. In doing this he hopes to render some service to humanity.

Continuing with his personal remarks he says that for a year he had occupied an important station at the Hospice des Enfants Trouvés in Paris, and observed with close attention the children in that institution. When a patient died he availed himself of the opportunity thus afforded to examine by dissection all the organs, and to ascertain the causes and seat of each disease. He says that in this manner has the wish of Morgagni been fulfilled. "I have been able by these methods," he says, "to compare the symptoms observed during life, with the anatomical lesions by which they have been produced."

Billard was guided and directed in his work by the great founders of pathology. The principal object of his book, he says, is to exhibit the peculiar characteristics of infant diseases, and to consider them in relation to the alterations which the organs have undergone. Finally, he says, "I have written this book with the independence of one who would not draw from existing doctrines anything, however positive, the truth of which could not be proved by established facts or by natural analogy. In this I have but imitated the great number of those who have cultivated science at the present day." This essay, then, carries with it the impress of the age and the spirit of contemporaneous philosophy. Those who read Billard will find his book a source of pathologic knowledge and clinical facts.

Before Billard, the influence of the teachings of Bichat and Laennec was already felt beyond the borders of France. Notably, a group of Irish physicians—among whom may be mentioned Cheyne, of Cheyne-Stokes fame; Corrigan, known through the type of pulse described by him, and Graves—practiced medicine on a pathologic foundation.

John Cheyne (1777-1836) wrote several chapters on diseases peculiar to children. He stated that the safest foundation for reasoning on the nature of disease is laid by anatomic investigation, and this, with little exception, formed the basis of his dissertations.

He refused to describe chorea in his textbook, because he had never seen a fatal case and consequently did not feel qualified to describe the disease.

As has been pointed out by John Ruhrah, in his excellent book, "Pediatrics of the Past," in the ancient literature, as well as in the writings of the Renaissance, were many gems of pediatric knowledge, mingled in the writings of the masters. In a more recent period, the contributions of Walter Harris, Thomas Thatcher, Nils Rosen von Rosenstein, George Armstrong and Michael Underwood were valuable treatises. But these writings are not of great concern in this presentation, because they were concerned with clinical descriptions and therapeutic speculation and were not founded on a knowledge of pathology.

Antoine Charles Ernest Barthez (1811-1891) of Paris and Frederick Rilliet (1814-1861) of Geneva studied in Paris in 1833. They published a three volume work on pediatrics with anatomic charts in 1843. Bokay speaks of this work as a source book of pediatrics, and the bible which was consulted by many generations of physicians. This book marks the beginning of the period of the scientific development of pediatrics.

This period marked the beginning of clinical investigation, and while the method of clinical observation based on postmortem studies was first carried out for pediatrics by Billard, it was faithfully continued by Barthez and Rilliet in their modern presentation.

Ernest Bouchut (1819-1891) was an expert in the use of the ophthalmoscope and in the diagnosis of nervous diseases. He was a medical historian and also wrote treatises on diagnosis as well as several books on pediatrics. The method of Billard was the one which he adopted, and his clinical descriptions were largely based on pathologic observations. He differentiated atelectasis from pneumonia and was one of the first to intubate the larynx with a long tube. In his writings and his teachings, he was alive to the thought expressed by the French school that pathologic anatomy was the key to the development of clinical medicine and pediatrics.

Armand Trousseau (1801-1867) of Tours was professor of the faculty of medicine of Paris and physician to the Hôtel Dieu. Trousseau was a student of Bretonneau and was inspired by the pathologic trend of the period. He was a far-famed clinical teacher and practitioner of great renown. His published lectures were translated into many languages and were eagerly read. With him, pediatrics was not a major branch. He described a sign for the recognition of tetany, extended Bretonneau's teachings on diphtheria, and performed tracheotomy. He considered pediatrics a part of general medicine. Garrison says of Trousseau's lectures that this was the last time that important pediatric contributions were published as a subsidiary portion of internal medicine, yet never perhaps under more brilliant auspices.

While great activity was going on in France in the development of pathology and internal medicine and the influence of both was felt by the new department of pediatrics, a new leader had arisen in Austria. With the advent of Carl Rokitansky (1804-1878) in the department of pathology in Vienna, scientific medicine in Austria and Germany felt a new impetus. As has already been noted, the Paris school of medicine was most advanced in the early nineteenth century. In England, Bright, Addison and Hodgkins studied nephritis, pernicious anemia and lymphatic diseases. It is true that in Germany a group of investigators were engaged in the pursuit of the fundamental sciences. Wunderlich, Henle, Johannus Müller and Theodore Schwann were eliciting new physiologic and anatomic facts, and attempting to correlate these in their relation to practical medicine.

The researches of these fundamental scientists were not well received at first because of the division of German medicine into different schools and sects.

Rokitansky entered into his work with great enthusiasm, keen judgment and descriptive ability. In his lifetime he performed more than 30,000 autopsies and gave many original descriptions, and no one since the time of Morgagni delved so deeply into the study of pathology at the autopsy table.

Most of Rokitansky's original studies were made with the unaided eye. Later, after being severely criticized by Virchow for neglecting microscopic studies, he investigated his tissues from the histologic standpoint, rewrote his handbook and deleted some of the fantastic theories of blastemas and crases that savored of humoral pathology. His studies included every branch and specialty of medicine. He differentiated between lobar and bronchopneumonia. He studied abnormalities of the fetus, atelectasis, the thymus gland and the urinary organs of the fetus and new-born. During the years 1842-1846, Rokitansky gave to the world his "Handbuch der Pathologischen Anatomie," in three volumes. He also published a monograph on diseases of the arteries in 1852, and a memoir on defects of the septum of the heart in 1875, the result of fourteen years of labor.

Rokitansky was an epoch making figure. Not only did he contribute largely to the development of the department of pathology, but he also extended the knowledge which had been initiated by Morgagni, and which had been further developed by the French school into a wider field. He showed that the accurate knowledge of clinical medicine depended on the study of pathology.

Vienna was the first place in the Germanic world in which the methods of physical examination, as taught by Corvisart and Laennec, were practiced.

The principal achievements of Josef Skoda (1805-1881) were due first and foremost to his cooperation with Rokitansky and to his interpretation of physical characteristics on the basis of studies in pathology. To him percussion and auscultation consisted in the application of the physics of sound in the use of these diagnostic methods.

Skoda, as well as Rokitansky, differed from the French school, particularly from the teachings of Laennec, in believing that these new methods of physical examination were significant only so far as they represented anatomic changes. Skoda considered pathologic changes of the first importance; clinical observations were secondary. He agreed with Rokitansky, who expressed himself in his textbook (1848) that pathologic anatomy was the foundation of medical knowledge and medical practice.

It is obvious that there is much truth in this thought, but, on the other hand, disease does not consist only in disturbance of structure, but also in disturbance of function. Nevertheless, Skoda should be considered a pioneer and pathfinder, and one who perfected rational methods of diagnosis, so as to enable his contemporaries and successors to interpret anatomic changes on the basis of physical observations.

The impetus which Rokitansky and Skoda gave to pathology and clinical medicine was soon followed by the division of medicine into many specialities. Internal medicine, physical diagnosis and numerous

minor branches were studied intensively in the Austrian school. A university chair of pediatrics was established in the Vienna Clinic. Under the influence of Ludwig Mauthner (1806-1858), St. Annen-Kinderspital, the third of its kind in the world, was established in 1858. After Mauthner's death, the institution was taken over by Franz Mayr (1814-1863). His directorship occurred during the period of the greatest progress of the Vienna school. He was an impressive teacher and commanded a large clinical material, developing into a keen student of his branch under the leadership of Rokitansky. As a model for his clinical studies, he took the works of Rilliet and Barthez in Paris, and Löschner in Prague.

A large student following came to him from near and far. Mayr should be regarded as the founder of clinical pediatrics in Vienna. He died in his forty-ninth year, and, though his period of active work was short, his influence was immeasurably large. He was the founder of the Vienna school with its elaborated semeiotics. A clinical investigation of congenital syphilis and an extended study of 594 cases of measles with complications, sequelae and epidemiology were part of his work. He also wrote on herpes, lichen, miliaria, erysipelas and erythema nodosum, and attempted to vaccinate against measles. In 1858, he became one of the founders of the *Jahrbuch für Kinderheilkunde,* which is still in existence. Obviously, the clinical teachings of the new Vienna school in pathology and internal medicine influenced Mayr in developing clinical pediatrics.

Fedor Alois Bednar wrote a treatise on the diseases of the new-born infant in 1850-1853 and a pediatric Lehrbuch in 1856. In the latter he says that he has been guided by the scientific and anatomic-pathologic investigations of the period. He deplores the fact that the therapeutics were not founded on scientific principles, and were therefore negligible, thus following the "nihilistic" teachings of Rokitansky and Skoda. He says, however, that the development of therapeutics will progress along scientific lines, and therefore recommends that remedies be studied in their physical as well as in their chemical properties, and in their effect on normal persons. Bednar seems to have sensed the modern trend of medical thought when he says that life should be viewed as the result of a series of vital and chemical processes, and, consequently, that the nature of the disease should be studied in the light of the alteration of these functions.

In the publication of his "Diseases of the New-Born," he may be compared to Billard, as a pioneer in this direction, because he based his clinical descriptions on pathologic studies of the material in the infant asylum at Vienna. Garrison quotes Jacobi as saying, "Bednar was one of the most original scientific pediatrists of Europe during his period."

Herman Wiederhofer (1832-1901) graduated in medicine in 1859. He served an internship in the Vienna Infant Asylum. When Franz Mayr became director of the St. Annen-Kinderspital, Wiederhofer was selected as first assistant. In 1862 he became privatdozent in the diseases of children, in 1866 assistant professor and in 1884 professor. For forty years he continued in these positions. He published papers on thymic abscess, hereditary syphilis and diseases of the umbilicus. In 1863, he succeeded Mayr as one of the editors of the *Jahrbuch für Kinderheilkunde*. His most important contributions were to Gerhardt's "Handbuch." His chapter on the diseases of the gastro-intestinal tract of infants and older children was written in collaboration with Hans Kundrat, who wrote the section on pathology. This was a classic contribution, and while the conception of this group of disorders has changed many times since the publication of the paper, it must be conceded that the clinical descriptions were keen and masterful. Wiederhofer was an excellent teacher, and students were attracted to him from every part of the world.

Contemporaneous with Wiederhofer were Ritter von Rittershain (1820-1883) of Prague, who described dermatitis exfoliativa, and his student, Alois Epstein (1849-1918), who subsequently became director of the infant asylum at Prague. Epstein was recognized as one of the outstanding authorities on diseases of infancy. The asylum at Prague became the Mecca for those who sought the opportunity of improving themselves in the pathology and treatment of infants. Adelbert Czerny and R. Fischl were pupils of Epstein.

Among the other early German and Austrian pediatricians of note, who combined a knowledge of the fundamental sciences and pathology with clinical pediatrics, were L. M. Pollitzer of Vienna, M. Schuller of Vienna, Johann Bokay, Sr., of Budapest, M. Kassowitz of Vienna, Löschner in Prague and his successor Johann Steiner, A. Hüttenbrenner of Vienna, Carl Gerhardt, A. Vogel of Dorpat, A. Baginsky, Harold Hirschsprung of Denmark, Rauchfus of St. Petersburg, Soltmann of Leipzig and Von Ranke of Munich.

Meanwhile, a successor to Armstrong and Underwood was found in England in the person of Charles West. West was born in London in 1816 and died in 1898. He graduated from St. Bartholomew's in 1833, having studied under Graves and Stokes. He resided in the hospital for two subsequent years and then studied a year at Bonn. Another year was spent in Paris, and he graduated at the University of Berlin in 1837, presenting an illustrated dissertation on the female pelvis. In Berlin he was influenced by the teachings of Johannes Müller.

In the beginning of his practice he devoted much of his energy to the study of obstetrics and delivered lectures on midwifery at St.

Bartholomew's in 1848, and on diseases of children at Middlesex Hospital in 1847. In 1852, West established the great Ormond Street Hospital for Children, which he actively directed for forty years. His book, "Diseases of Infancy and Childhood," was the prevailing textbook in England for many decades, and Henoch translated it into German.

His clinical studies of children undoubtedly were based on the teachings of the French school, as well as on the principles of Haller and Johannes Müller, which he absorbed during his residence in Germany. In 1840, he translated Müller's essays on the structure of cancers and tumors.

West developed into an excellent clinician, traveling the same path as many of his predecessors, by first practicing and teaching obstetrics and then combining, perhaps in his case in a major way, the practice of pediatrics. His fundamental training, however, was in pathology, acquired in France and Germany, and whatever success he may have attained must be ascribed in great measure to his education in this branch.

While events of a pathologic and clinical nature were progressing in France, Austria, and, to a lesser extent, in the British Isles, Germany became the scene of a new activity. In the early part of the nineteenth century, German medicine was divided into numerous philosophic schools, among which there was much dissension. Each presented a speculative form of philosophy, theoretical and mystical in nature, without a true scientific foundation. The unification of medicine was brought about when the various speculative theories were replaced by the pursuit of the biologic sciences. The anatomic studies were pursued by Johannes Friederich Meckel (1714-1774); Friedrich Schlemm (1795-1858), professor of anatomy and surgery at Berlin; Friederich Gustav Jacob Henle (1809-1896), a pupil of Johannes Müller, and Theodore Schwann (1810-1882). Purkinje studied the physiology of the sense organs; Friedman and Gmelin the physiology of digestion, and the Weber brothers the circulation, acoustics and muscular movements. In France and England, Flourens, Magendie, Bell and Marshall Hall advanced this new science.

The new era was introduced by Johannes Müller (1801-1858). Müller was a genius of rare quality and investigated nearly every branch of the biologic sciences. To do this required that he make a large number of original researches. He verified Bell's law of the different functions of the anterior and posterior roots of the spinal nerves and the theory of reflex action. His investigations on the physiology of the blood and the discovery of the lymph heart of amphibia were only a few of his contributions. His "Handbook of Physiology" was published in 1840, and covered the whole field of

the functions of animal and human life. He also made valuable contributions on comparative anatomy, systematic zoology and paleontology.

His contributions to pathology are important, too. Practically all the distinguished German scientists of this period were his students; and they acknowledged that through him they acquired their scientific methods and from him received the inspiration which gave them the grasp of modern medicine.

I have already referred to the influence of the new medicine in Austria. It fell to the fate of Johannes Lucas Schönlein (1793-1864) to initiate a new era of clinical medicine in Germany as Johannes Müller had introduced new aspects of the biologic sciences. Schönlein wrote and published little, but through his labors, the philosophic aspect of medicine was superseded by the natural science view. He soon became possessed with the importance of percussion, auscultation and chemical and microscopic examination at the bedside. It was a far step in advance for him to hold his clinics in the German language instead of Latin. This new spirit of medicine, introduced into Germany by Schönlein, was pursued by his numerous students and followers.

The most distinguished of them and the one who was to exert the greatest influence in the development of medical thought was Rudolf Virchow (1821-1902). He emulated the teachings of Johannes Müller, his master. He was the reformer in the field of general and pathologic anatomy. Through him, humoral pathology as a factor in the nature and cause of disease was forever abolished. Even Rokitansky's crasis theory gave way before his scrutinizing and painstaking investigations.

Cellular pathology became the keynote of this master's teachings. He sought the location and nature of disease in the alteration of the cellular elements. Most of the conceptions of pathology that are held today were discovered by him. All modern pathology bears the stamp of the cellular doctrine, as well as of Virchow's genius. There was hardly any field of pathology that he did not thoroughly investigate.

Of particular interest to the pediatrician were his studies on thrombosis in the new-born. He also observed the uric acid infarcts in the fetus and the new-born, and found them common between the second and twentieth day after birth. He considered their presence a physiologic occurrence. Three cases of cystic kidney in a family in which four other children were healthy were reported by him. He published a study on icterus of the new-born; he thought that this condition was catarrhal in nature, and associated with gastroduodenal catarrh. In his study of icterus he encountered only one case of congenital atresia of the bile ducts. Cretinism interested him, and he made detailed postmortem studies including the histology of the various organs. He came to the erroneous conclusion that cretinism was due to early synostosis of

the bones at the base of the skull, and in his first writings he failed to be convinced of any association between the thyroid gland and cretinism.

He discovered the nature of leukemia and laid the foundation for all the teachings on thrombosis and embolism. He taught that rickets was exclusively a disease of growing bone and, consequently, was a disorder peculiar to childhood. It is only natural that this genius and pathfinder should have stimulated students in every department of medicine. The pathologists who were his contemporaries and successors were his eager pupils. The internists also came under the influence of his teachings, and learned the nature of disease through his investigations.

Here then is the essential point. At the outset, the question was asked: *What was the influence of pathology on the development of pediatrics?* As has already been noted Billard, Barthez and Rilliet, Bretonneau and Bouchut began the study of organic disturbances of the infant and child on the basis of the teachings of Morgagni, Bichat, Corvisart and Laennec. Further, Austrian pediatrics developed as the result of the teachings of Rokitansky and Skoda.

As an illustration of the poverty of original German pediatrics of this period, it may be pointed out that as late as 1848 Underwood's work was translated into German. Barez was a general practitioner who taught pediatrics in Berlin as early as 1839.

Pediatrics is one of the youngest of the special branches of medicine. In an earlier period, the new-born and young infants were treated by the internists. With the development of pathologic anatomy and histology, and with the perfection of the methods of physical examination, it was soon learned that certain diseases were peculiar to young life. It had already been pointed out that there were physiologic and anatomic differences between the infantile and adult organisms. Before the middle of the nineteenth century, Austria and Germany had practically no children's hospitals. The great Ormond Street Hospital had recently been organized in England, and a children's hospital had previously been established in France.

Children's specialists were practically unknown, except in a few isolated instances already recorded. In 1868, at one of the early meetings of the German National Medical Society, a separate section for diseases of children was founded. The champion of this section, Steffen of Stettin, lamented at the time that separate departments for instruction in the diseases of children did not exist in universities. It was deplored that pediatrics was the step-child of internal medicine. The internists were reluctant in most instances to relinquish the pediatric material, as they desired it for clinical teaching.

Pediatrics became more firmly established, in proportion as the knowledge of pathology in this department increased, and as more

detailed study and more careful clinical descriptions of the course of various diseases were made.

At the inception, there were not any large children's hospitals where specialists could be trained and, consequently, the pioneer teachers and investigators were trained primarily in the pathologic institutes and clinics of internal medicine. Indeed, the first and the best of the early pediatricians of this modern period emerged from the clinic of internal medicine to the special field of pediatrics.

Thus, Eduard Henoch (1820-1910) was trained in physiology and in Virchow's school of pathology, and he also was indebted to Traube, the first experimental pathologist. He imbibed the traditions of Schönlein, who was his teacher, and served as assistant for seven years to the celebrated Romberg, who was his uncle. He graduated in his twenty-second year, and his thesis was on cerebral atrophy. After his graduation a long time was spent in Paris, and he was undoubtedly influenced by the enthusiastic devotees of the French pathologic and clinical schools. He wrote on the comparative pathology of motor nerves, and in 1853 published a three volume work on abdominal disease.

In 1860, he established in his private dwelling a clinic for diseases of children. Thus, it is observed that at this time he began actively to study and teach the diseases of childhood. In 1861, he published his "Beitrage zur Kinderheilkunde," and in 1864, he translated Charles West's book on "Diseases of Childhood." In 1872, he was given charge of the polyclinic at the Charité and became professor of diseases of children, in which capacity he continued until 1893.

Henoch laid the foundation for modern pediatrics in Germany. Before his time, no such distinct specialty existed. He also founded the first university pediatric clinic in Germany.

Otto Heubner (1843-1926) also entered pediatrics through the route of internal medicine and pathology. Heubner was particularly indebted to Wunderlich, one of the most progressive internists of his day. In order to show his various interests it may be stated that Heubner worked in a cholera hospital in Leipzig, at which he did some experimental work on the effect of camphor on the frog's heart. He also studied dysentery, clinically and pathologically.

In his thirty-fourth year, Heubner described endarteritis obliterans syphilitica. In 1876, he instituted an outpatient service for sick children, visiting the patients in their homes. In his autobiography, he describes the early meetings of the section for diseases of children of the German National Medical Society. He names a small group and observes that most of the members of the section became specialists after long service in internal medicine. This implies also that they were trained in pathology, under either Virchow, the master, or one of his students.

Heubner trained a group of assistants who came to occupy important places in the pediatric world as teachers and investigators. Among these should be mentioned Finkelstein, Erich Müller, Stöltzner and Salge.

Exactly thirty years ago, Dr. S. S. Adams, in his presidential address before the American Pediatric Society, gave an interesting and valuable historical account of the evolution of pediatric literature in America. This address also took account of the development of pediatrics, based on pathologic progress.

Dr. W. W. Gerhard of Philadelphia has already been referred to as a student of the French school, and particularly of Louis. The traditions of pathology and clinical medicine were brought to America by him. He made careful autopsies and wrote detailed clinical descriptions. Fatal cases of measles, tuberculosis and meningitis with autopsy were reported by him. He also studied the pathology of croupous pneumonia in children.

Others made contributions to the literature. James Stuart, 1806, conducted an autopsy on cholera infantum. James Jackson, 1812, reports a similar condition with autopsy results.

Aside from those mentioned, notable contributions were not made until the middle of the nineteenth century. An account of pediatrics in America from the pathologic standpoint could not be written without referring to the epoch making contributions of Abraham Jacobi (1830-1919). He recognized the progress that modern pediatrics had already made on European soil. He was always a close student and an original thinker. The newer ideas of pathology in pediatrics were introduced into American practice by him.

Dr. J. Lewis Smith of New York (1827-1897), Jacobi's contemporary, contributed a textbook in 1858, in which he said that the material contained therein did not disregard the opinion of previous writers, though he depended on his own clinical observations and inspection of the cadaver.

In more recent times Thomas Morgan Rotch (1849-1914) wrote an important book on pediatrics (1896).

Luther Emmet Holt (1855-1924) prepared himself as a practitioner and teacher by long service in the study of pathologic material in infants and children. Based on an accumulation of pathologic and clinical facts, his epoch making textbook was published in 1896.

His student, John Howland, was similarly trained in pathology, though he eventually added chemistry to his equipment.

One might continue discussing personalities, but it is obvious that the progress in medical learning was everywhere the same. The cloak of mysticism, speculation, philosophic theorization and sectarianism gave way slowly but surely to the advances in the knowledge of the biologic sciences. Descriptive anatomy and physiology led the way, and

pathologic anatomy, in every branch of medicine, became the basis for the study and clinical recognition of disease processes.

While pathologic anatomy was the cornerstone on which all modern medicine was founded, an equally important epoch was initiated by the discoveries of Pasteur and Koch, in the field of bacteriology, an increasingly important branch of general pathology. It would be superfluous to enumerate, at this time, the remarkable influence of these discoveries on the progress of medicine. The nature and causes of disease hitherto unknown were unraveled. The success in the prevention and treatment of disease would in many instances have surpassed the dreams of the medieval astrologers, necromancers and medical magicians.

It has been the object of this paper to show how pediatrics developed as a result of the increase in the knowledge of pathology. This has been done by tracing the efforts of those individuals whose genius led them to disentangle the intricacies of the fundamental biologic sciences, and also by giving an account of those gifted leaders who founded clinical medicine by utilizing the knowledge obtained from the fundamental sciences. New light is being shed on medical problems by the application of chemistry, physics, bacteriology and immunology; but the fact remains outstanding that a proper conception of disease processes, a valid clinical interpretation and a mental picture of disease depends on a knowledge of the morbid changes that have occurred in organs and cells. It is true, as has already been said, that disturbed function may not be discovered by dissection or microscopic examination of tissues; nevertheless, scientific medicine, including modern pediatrics, was possible only through an increasing knowledge of morbid anatomy.

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RESPIRATORY ANAPHYLAXIS

SENSITIZATION, SHOCK, BRONCHIAL ASTHMA AND DEATH INDUCED IN THE GUINEA-PIG BY THE NASAL INHALATION OF DRY HORSE DANDER *

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Several years ago, one of us [1] studied a group of children suffering from bronchial asthma, the cause of which was traced to rabbit hair. In none of these cases was it possible to obtain any hereditary evidence of protein sensitivity; the opinion was therefore expressed at that time that the sensitization had been acquired through the inhalation of dry dust resulting from the rabbit hair which was present in pillows, comfortables, toys, clothing and other articles.

In order to prove this hypothesis, we felt it necessary to produce in an animal a state of protein sensitivity through the direct inhalation of a dry animal emanation, and, further, to reproduce the symptom-complex of bronchial asthma.

MATERIALS AND METHODS USED

In approaching this work, we were confronted with the following considerations: first, the choice of an animal in which this mechanism could be reproduced; second, the necessity of reproducing the entire mechanism with a dry, dust-producing animal emanation; third, the preparation of a solution of this dry substance which could be proved to be anaphylactogenic and also harmless for intravenous injection.

Choice of Animal.—The guinea-pig was our choice of animal because respiratory anaphylactic phenomena can be elicited in it with great ease and regularity.

Dry, Dust-Producing Animal Emanation.—Horse dander was the substance chosen because it is a common causative factor in a large group of cases of asthma, because it is not species-related to the guinea-pig, and because it lends itself to further experimentation which we have undertaken with relation to horse hair, horse serum and other substances.

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1. Ratner, B.: Rabbit Hair Asthma in Children, Am. J. Dis. Child. **24**:346 (Oct.) 1922.

Method of Preparing Dry Horse Dander.—Horse combings were obtained for us by grooms at Durland's Academy.[2] These combings were collected on large sheets of paper, were free from horse manure, and, with the exception of a stray piece of straw, were also free from other extraneous matter. The dander was a light gray powder of sticky consistency, intimately mixed with fine hairs.

We dissolved out the fat with ether, and the dander was separated from the hair and grit by successive decantations onto filter paper. Then the dander, which was practically free from fat and hair, was thoroughly washed with ether until no visible color could be detected in the washings, and finally extracted with a Soxhlet apparatus. It was air dried, and a fine gray powder resulted, which was used in our inhalation experiments and in the making of our dander solution.

Among the previous workers with horse dander, Friedberger and Kamio [3] and Busson and Ogata [4] make no mention of defatting their dander or separating it from the hair and grit. A partial separation was achieved by Wodehouse,[5] who sifted out the hair and grit from the dry material. The final step—the defatting with ether—was added by Longcope, O'Brien and Perlzweig [6] and by Coca and Milford.[7] This defatting is practically essential to make a clear dander extract.

Friedberger and Kamio, who were the only workers to use dry dander for inhalation experiments, used it in the original state. In some of our early experiments, we found that the dander as obtained from the original source did not produce the dust-laden atmosphere that we believed essential in our work.

Our first steps in the approach to our problem are presented to show that we were proceeding with an animal emanation which was so treated as to make it particularly suitable for the experiments in hand, but the nature of which was in no way changed metabolically.

Solution Used.—In order to prove that the results of our experiments with the inhalation of dry dander were valid, it was necessary for us to use some accepted method of producing anaphylactic phenomena. For this, it was essential to make an anaphylactogenic solution which could safely be used for intravenous injection.

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2. Durland's Academy boards horses which are exceptionally well-groomed. The stables and stalls are all that can be desired from the standpoint of cleanliness.

3. Friedberger, E., and Kamio, T.: Gelingt es, beim Meerschweinen experimentelle Beziehungen zwischen Asthma und Anaphylaxie nachzuweisen? Ztschr. f. Immunitätsforsch. u. exper. Therap. **37**:379, 1923.

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7. Coca, A. F., and Milford, E. L.: Studies in Specific Hypersensitiveness: XVII. The Preparation of Fluid Extracts and Solutions for Use in the Diagnosis and Treatment of Atopic Conditions, J. Immunol. **10**:555 (May) 1925.

Method of Preparing Horse Dander Solution.—The fat-free and hair-free dander obtained in the manner described was soaked in hundredth normal solution of potassium hydroxide (proportion: 1 Gm. of dander to 10 cc. of KOH) at body temperature for an hour and three quarters. A muddy solution with a moderate amount of undissolved sediment was obtained. This was filtered, centrifugalized and refiltered through paper pulp and animal charcoal, and finally was passed through a sterile N Berkefeld candle. The resulting solution was clear, amber-colored and sterile.

Our solution gave the various protein color reactions and was precipitated by mineral acids and alkaloidal reagents. The analysis of the nitrogenous content was as follows:

Total nitrogen	144 mg. per 100 cc. of solution
Nonprotein nitrogen	46 mg. per 100 cc. of solution
Protein nitrogen	98 mg. per 100 cc. of solution

The original p_H of our solution was always above 8, but whenever it was used for intravenous injection, it was adjusted to a p_H of 7.4. We have found, as have Longcope, O'Brien and Perlzweig, that the solution becomes more alkaline on standing, so that readjustments had to be made when a given solution was to be used on more than one day. However, we have adhered strictly, with but few exceptions, to using a fresh solution for each day's experiments. We are not certain that the fine adjustment of the p_H of our solution is absolutely essential, because in a large number of preliminary experiments we did not adjust the p_H, and our results, from an anaphylactic standpoint, were not different from those obtained with the adjusted solutions.

It is probable that we obtained a larger amount of nitrogen than did Longcope and his co-workers in their solution, because we made a more nearly complete separation of dry dander and other extraneous matter, thereby obtaining a greater proportion of dander per gram from which to extract.

In the making of a dander solution Coca,[8] Friedberger and Kamio [3] and Longcope, O'Brien and Perlzweig [6] used Coca's extracting solution (1922), with slight variations in method. In 1925 Coca and Milford [7] published the description of an improved solution, but they are the only ones who have used it for dander extraction. An alkaline extract of potassium hydroxide was used by Wodehouse [5] and one of soda lye by Busson and Ogata.[4] Friedberger and Kamio used physiologic sodium chloride in some instances. Coca, Coca and Milford, and Longcope, O'Brien and Perlzweig were the only ones to take precautionary measures for sterilization by passing the solutions through a Berkefeld candle.

8. Coca, A. F.: Studies in Specific Hypersensitiveness: V. The Preparation of Fluid Extracts and Solutions for Use in the Diagnosis and Treatment of the Allergies with Notes on the Collection of Pollens, J. Immunol. **7**:163 (March) 1922.

Friedberger and Kamio made no attempt to clear their solution of foreign particles by centrifugalization or filtration before using it for intravenous injection. They have cited examples of peritonitis following some intraperitoneal injections of their unsterilized solutions. These two facts alone tend to vitiate any of their results.

As Busson and Ogata made up their solution for the entire series of experiments at one time, their work is open to criticism. It is well known that protein extracts are unstable in solution, and when the same solution is used over a period of several months, the results can hardly be comparable.

Our solution is comparable to that of Wodehouse, but differs in that we made our extraction at body temperature.

In our extracting method we used body temperature and a weak alkaline solution. We made no attempt to consider the question of salts and other chemical problems. We were primarily interested in demonstrating a biologic mechanism, knowing as we do that a person with asthma inhales an epidermal substance at body temperature, presumably through an alkaline mucous membrane.

Hanzlik and Karsner [9] have shown that intravenous injections of many different substances may bring about embolic anaphylactoid phenomena. Wells [10] also objects to the intravenous route in anaphylaxis work for the same reason.

We believe that our solution is incapable of producing emboli, because we have used material freshly sterilized with a Berkefeld candle and therefore devoid of emboli-producing particles.

ANAPHYLACTOGENIC PROPERTIES OF HORSE DANDER

Cooke, Flood and Coca [11] have actively sensitized guinea-pigs to horse dander. Walker [12] obtained a positive complement-fixation reaction in persons who have acquired asthma from contact with horses with an extract of horse dander used as an antigen. Wodehouse [5] has shown that the various proteins extracted from horse dander give positive skin reactions in sensitive horses with asthma. Horse dander, by the impetus of the work of these investigators, has been used continuously for testing the sensitivity of patients with asthma to this substance.

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In spite of this evidence, Friedberger and Kamio [3] were unable definitely to sensitize guinea-pigs with extracts of horse dander, and they state that horse dander is not a sensitizing substance.

During the progress of our work, however, Busson and Ogata [4] refuted the conclusions of Friedberger and Kamio, and were convinced that they did sensitize guinea-pigs with an extract of horse dander.

Shortly after this work, Longcope, O'Brien and Perlzweig [6] showed that guinea-pigs could be made highly sensitive to an extract of horse dander; sensitized guinea-pigs died in anaphylactic shock when the extract was injected intravenously, and the uteri of sensitized virgin guinea-pigs responded in a characteristic manner with the Dale method. These investigators further believed that they were able to desensitize these animals to this extract. They also state that the sensitization to horse dander is specific, and shows no relationship to its homologous horse serum.

Independent of the latter investigators, we had also been at work on experiments to prove that the dry substance which we were using to sensitize our animals through the respiratory tract was anaphylactogenic. In order to prove that the inhaled substance was an anaphylactogen, it was necessary for us to make a solution of this substance.

Our extract was uniformly anaphylactogenic in about 100 animals, despite the fact that we used a freshly prepared solution for each day's experiments. Whenever a solution was used on a particular day, it was controlled. That the solution was capable of sensitizing, as well as of producing shock, was shown when we used the same solution on the same day, to induce shock in previously sensitized animals, and also to sensitize animals for future experiments.

Doses as small as 0.1 cc. given intravenously caused acute anaphylactic death, and amounts of 0.2 cc. given intraperitoneally were adequate for sensitization.

When large quantities of this solution were used on guinea-pigs of moderate size, there was evidence of primary toxicity in certain instances. Even though pigs of various sizes could tolerate intravenous injections as large as 5 cc., we found that when we used 1.5 cc. in smaller pigs, we occasionally obtained mild symptoms of irritability. On account of the anaphylactic death obtained when large doses were used, and on account of the irritability when 1.5 cc. was used, we decided on 1 cc. as the maximum amount for intravenous injection in our experiments, since at no time have we encountered any primary ill effects from this quantity. The same primary toxicity does not occur with intraperitoneal injections.

We attributed this primary toxicity to our extract, and not to the alkali, since control injections intravenously with from 3 to 5 cc. of hundredth normal solution of potassium hydroxide were perfectly tolerated.

Longcope and his co-workers conclude, from their experiments, that horse dander is anaphylactogenically specific, and does not give crossed reactions with horse serum. We [13] cannot concur with these investigators, as we have shown definite crossed reactions between these two substances. This relationship to horse serum will be the subject of another paper, and is merely noted here as a part of this general discussion on the properties of horse dander extract.

In figure 1, we have an example of a positive contraction of the uterine strip of an animal that had been sensitized with dander extract.

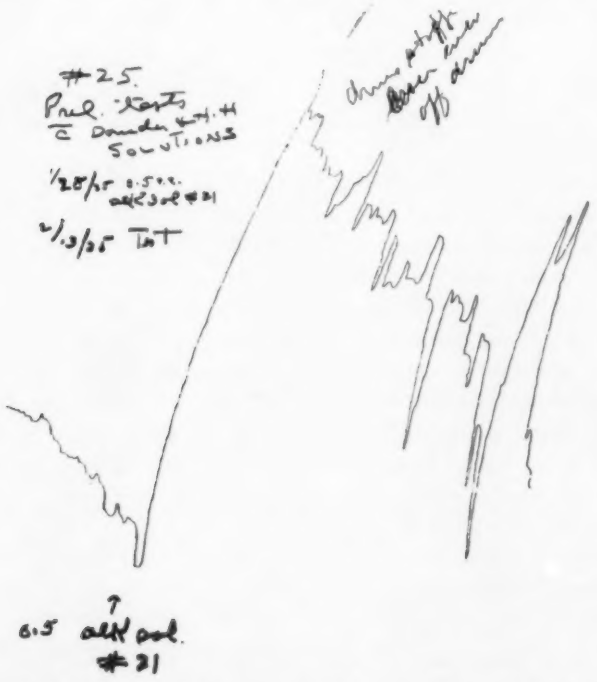

Fig. 1.—Curve shows positive contraction of uterine strip of guinea-pig sensitized with 0.5 cc. of dander extract, intraperitoneally.

A guinea-pig was sensitized with 0.5 cc. dander extract, intraperitoneally; sixteen days later, the uterine strip was suspended in a 300 cc. oxygenated bath of Locke's solution. On Feb. 13, 1925, 0.5 cc. of the alkali extract was instilled in the bath at the point of the arrow. There was an immediate and marked contraction of the strip, the lever completely going off the drum. The uterus thereafter showed a marked irritability. This appears to be a specific reaction.

13. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: The Anaphylactogenic Character of Horse Dander and Its Crossed Relationship to Horse Serum, Proc. Soc. Exper. Biol. & Med. **23**:16 (Oct.) 1925.

In figure 2, we have another example of a positive contraction with the uterine strip of an animal sensitized to dander extract; in this tracing, there are several further facts brought out, which prove beyond doubt that the reaction is specifically anaphylactogenic. A guinea-pig was sensitized on June 10, 1925, with 0.2 cc. of dander extract intraperitoneally. On June 29, nineteen days after the sensitizing dose, the right uterine horn was suspended in a 300 cc. oxygenated bath of Locke's solution, which was kept between 37 and 40 C. Two cubic centimeters

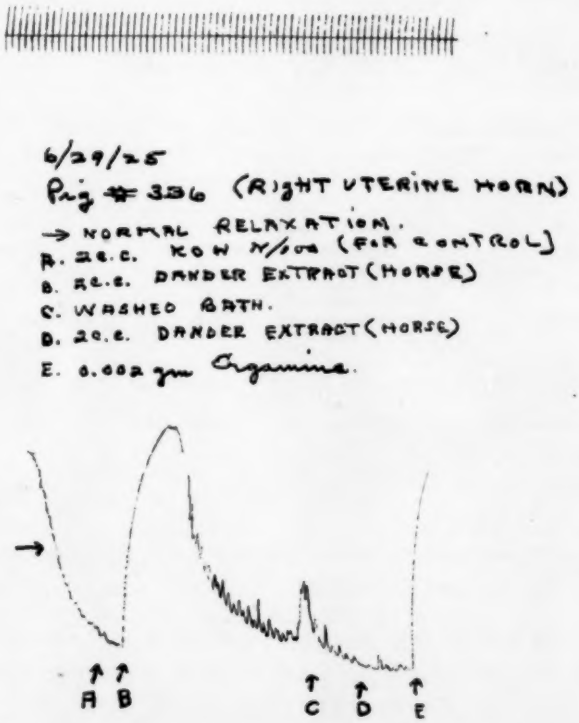

Fig. 2.—Curve shows the contractions of the uterine horn of a guinea-pig in a 300 cc. oxygenated bath of Locke's solution to which other substances were added. *A* is the point at which a normal solution of potassium hydroxide was added to the bath, giving no contraction; *B* shows immediate contraction on addition of dander extract; *C* marks the return to the original base line twenty-five minutes later, after the effect of the danger extract subsided; *D* marks the point of the second instillation of dander extract after ten minutes, with no contraction; *E* is the point at which ergamine was added, giving an immediate contraction. Minute markings at the top of the chart indicate the time elapsed between changes.

of normal solution of potassium hydroxide, when put in the bath, proved to be nonirritating (*A*); 2 cc. of dander extract gave immediate contraction (*B*); the bath was washed twice with fresh Locke's solution after twenty-five minutes, during which the muscle resumed its original base

line (*C*); after ten minutes, 2 cc. of dander extract was again placed in the bath (*D*), and there was no contraction. This lack of response indicates one of two things: that of natural debility of the muscle, i. e., an inability to respond to any stimulus, or a specific state of desensitization due to an exhaustion of the antibodies as a result of combination with the first installation of dander extract. In order to prove the latter analysis of *D*, we instilled 0.002 Gm. of ergamine acid phosphate—a normal uterine contractor—and an immediate contraction was elicited (*E*). This proves that at *D* we have a state of specific desensitization, and at *B* a specific anaphylactic contraction. Another point of interest in this tracing, is the fact that this uterine strip, which was

TABLE 1.—*Anaphylactogenic Character of Dander Extract*

No.	Weight	Date	Cc. of Dander Extract	Cc. of Fat Extract*	Route	Days Elapsed	Date	Cc. of Dander Extract	Cc. of Fat Extract	Route	Results
27	300	1/28/25	0.5	...	Intraperitoneal	16	2/13/25	2.5	...	Intraperitoneal	Death†
3	340	1/ 7/25	0.5	...	Intraperitoneal	16	1/23/25	1.0	...	Intraperitoneal	Death
5	350	1/ 7/25	...	0.5	Intraperitoneal	16	1/23/25	...	2.0	Intraperitoneal	Negative
						19	1/26/25	2.0	...	Intraperitoneal	Negative
299	555	5/27/25	0.2	...	Intraperitoneal	14	6/10/25	0.8	...	Intravenous	Death
333	355	6/10/25	0.2	...	Intraperitoneal	16	6/26/25	1.0	...	Intravenous	Death
204	350	6/29/25	1.0	...	Intravenous	Control.....					Negative
414	280	9/30/25	1.0	...	Intravenous	Control.....					Negative

* Fat extract is alkali extract of the fat removed from original dander, prepared in same manner as dander extract.
† Death with typical anaphylactic lungs.

naturally weak and the best type to use, is shown to have consummated its complete contraction at *B*, by the fact that at *E* the contraction was no greater. (The left uterine horn presented the same observations as shown here.)

Table 1 gives the results of several experiments picked at random from more than 100 similar experiments. It will be noted that animals can be sensitized with dander extract, and that death is brought about in these animals by intraperitoneal and intravenous injections; control animals show no reaction. Animal 5 shows the absence of an anaphylactogen in the fat extract. The line below shows further, by the use of dander extract, that no anaphylactogen was present in the original sensitizing injection of fat extract.

Table 2 demonstrates that the anaphylactogenic substance present in horse dander can also serve as a means of diagnosing a state of allergic sensitivity in a human being with asthma. In table 2 there are examples

of positive skin reactions to horse dander in two children suffering from asthma. It will be noted that the positive allergic skin reactions were obtained by the ordinary scratch method with dander, in both its natural and extracted forms.

We believe that the facts shown in these tables adequately corroborate the view that horse dander is an anaphylactogen. Further, the anaphylactogenic substance in horse dander can produce both anaphylaxis in the guinea-pig and allergic skin reactions in the human being.

ANAPHYLAXIS INDUCED THROUGH THE RESPIRATORY TRACT

History.—Friedberger,[14] in 1911, succeeded in producing in guinea-pigs what he called anaphylactic pneumonia. This was brought about by subjecting animals that had previously been sensitized to horse serum, to a spray of this substance.

Busson,[15] working independently of Friedberger, in the same year, published a larger list of experiments, stating that he had been successful

TABLE 2.—*Allergic Skin Tests on Two Patients Who Acquired Asthma from Contact with Horses*

Patient	Age	Date	Test	Arlington*	Squibb*	Original Dander	Defatted Dander	Dander Alkali Extract
F. T.	12 years	12/13/24	Scratch	+	+	+	+	+
A. W.	3 years	12/16/24	Scratch	+	+	+	+	+

* Commercial dry horse dander supplied by Arlington Chemical Company and Squibb Chemical Company.
+, positive skin reaction.

in sensitizing the air passages of the guinea-pig by inhalation of diluted cattle serum, thus producing hypersensitiveness.

Sewall,[16] in 1914, sensitized animals by nasal instillation of horse serum.

In 1915 and 1916, Sewall and Powell[17] presented some further evidence of this nasal sensitization. They demonstrated that on further treatment with horse serum, the animals developed symptoms of bronchial asthma. They showed the oral route to be ineffective.

14. Friedberger, E.: Die Anaphylaxie mit besonderer Berücksichtigung ihrer Bedeutung für Infektion und Immunität, Deutsche med. Wchnschr. **37**:481 (March) 1911.

15. Busson, B.: Ueber Eiweiss Anaphylaxie von den Luftwegen aus, Wien. klin. Wchnschr. **24**:1492 (Oct.) 1911.

16. Sewall, H.: Some Relations of the Brain and of the Olfactory Apparatus to the Processes of Immunity, Arch. Int. Med. **13**:856 (June) 1914.

17. Sewall, H., and Powell, C.: Studies on the Relations of the Hypersusceptibility and Insusceptibility Induced in Guinea-Pigs by the Instillation of Horse Serum Into the Nose, Arch. Int. Med. **16**:605 (Oct.) 1915; The Conditions and Characters of Immunity Produced in the Guinea-Pig by Instillation of Horse Serum into the Nose, J. Exper. Med. **24**:69, 1916.

In 1917, Sewall [18] stated that he had produced all the features of bronchial asthma in the guinea-pig, and that the origin of this asthma is anaphylactic. He also believes that this is not a local hypersensitiveness, but is of general nature.

Ulrich,[19] in 1918, was the first to attempt to sensitize guinea-pigs with a dry substance. He was mainly concerned with the problem of hay-fever, using ragweed pollen for his experiments, and concluded that the clinical manifestations of hay-fever could be reproduced in laboratory animals. He also voiced the opinion that horse serum, as a nasal sensitizing agent, was not satisfactory. This criticism of the work of Sewall was not justifiable, as the evidence presented was not adequate.

Besredka,[20] in 1920, showed definitely, for the first time, that serum introduced into the larynx was absolutely harmless for normal animals, but fatal for sensitized animals. He also states that it is comparable to the introduction of serum intravenously, and that the trachea adapts itself to the absorption of large quantities of serum.

He suggests the use of a concentrated serum through this route for therapeutic measures in man.

In 1922, Petragnani [21] sensitized and produced shock in guinea-pigs with sheep serum through the nasal mucosa. This work is of great value, as every attempt was made to prevent the seepage of serum through the laryngotracheal passages. This was accomplished by holding the animals upside down and instilling the serum nasally.

Friedberger and Kamio,[3] in 1923, approached the problem from the standpoint of linking up the idiosyncrasy of asthma in the human being with anaphylaxis in animals. They voice serious objections to Coca's viewpoint that these two processes are dissimilar, and believe that there is a relationship between asthma and anaphylaxis. They have failed, however, in their experiments, to link up these two conditions.

Their experiment of greatest interest to us was that in which animals, sensitized to dander extract, were subjected to a spray of dry dander. They failed to produce shock or to kill animals by this exposure to dry dander.

Busson and Ogata [4] reported, in 1924, that they did not accept the conclusions of Friedberger and Kamio, and believed that they exposed their animals to dry dander for too short a period of time. However, Busson and Ogata made no attempt to continue Friedberger and Kamio's

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18. Sewall H.: Experimental Asthma in the Guinea-Pig, J. Lab. & Clin. Med. **2**:874, 1917.

19. Ulrich, H. L.: Experimental Pollinosis (Preliminary Report), J. Immunol. **3**:453 (Nov.) 1918.

20. Besredka, A.: De l'action des serums par la voie respiratoire, Ann. de l'inst. Pasteur **34**:51, 1920.

21. Petragnani, G.: Anafilassi e deanafilassi per la via nasale, Policlinico sez. med. **26**:446, 1922.

work with dry dander. They adhered strictly to the use of a solution of horse dander, which was introduced in the form of a heavy spray into the cages in which the animals had been placed.

They also sensitized animals by spraying them. After a prolonged spraying, for many days, they produced death in the animals with typical anaphylactic lungs and fall in temperature.

Sternberg,[22] in 1924, believed that Petragnani was the only investigator to show absorption of a colloidal substance through the nasal mucous membrane. He stated that the work of Besredka, Busson and Friedberger on the sensitization by absorption of vaporous protein, was not significant, since they did not prove whether the material was taken up by the mucous membrane of the introductory air passages or by the mucous membrane of the alveoli of the lung.

Sternberg concluded from his own work that the absorption of colloidal protein did not take place to a noticeable degree in the healthy mucous membrane of the trachea, but that it was absorbed by the alveoli of the lungs.

Jones,[23] in 1924, was able to sensitize guinea-pigs intratracheally with small amounts of horse and cow serum, but was not able to produce shock in animals by intratracheal injections. He believed, therefore, that small amounts of foreign serum are absorbed slowly through the lower respiratory tract, which accounts for the inability to produce shock.

Van Leeuwen, Bien and Varekamp [24] state that they have succeeded in sensitizing animals by the inhalation of parasite-infected oats, and also claim that their animals showed what they regarded as allergic manifestations shortly after, i. e., within three or four days from the first contact with the contaminated oats. They suggest that an "asthmogen," and not an anaphylactogen, is the cause of these symptoms.

One cannot fully understand their experiments with dogs, in which they compare the anaphylactic reactions of dogs with those of guinea-pigs. It is well known that the dog's anaphylactic reaction is totally different, resulting in collapse, fall in blood pressure and bleeding into the liver.

Van Leeuwen,[24] quoting some unpublished work that he did in collaboration with Landsteiner, states that they were unable to produce shock in previously sensitized animals by the inhalation of pollens and dried horse serum.

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22. Sternberg, H.: Beitrage zur Physiologie und Pathologie der Schleimhaut der oberen Luftwegen. II. Zur Resorptionsfähigkeit der Schleimhaut der Luftwege, Ztschr. f. Hals-, Nasen- u. Ohrenh. **8**:275, 1924.

23. Jones, F. S.: The Effects of the Intratracheal Administration of Foreign Serum, J. Exper. Med. **40**:63 (July) 1924.

24. Van Leeuwen, W. S.; Bien, Z., and Varekamp, H.: Experimentelle allergische Krankheiten (asthma bronchiale, Rhinitis vasomotoria), Ztschr. f. Immunitätsforsch. u. exper. Therap. **40**:552, 1924.

In October, 1925, we [25] published a preliminary report of the present work.

Alexander, Becke and Holmes [26] are the most recent investigators to study the problem of anaphylaxis induced through inhalation. Like the overwhelming majority of previous workers, they have worked with solutions. They have fully corroborated the work of Friedberger, Busson, Sewall and Powell, Petragnani, and Busson and Ogata, and have adhered to the method of Busson—spraying in cages—as opposed to the method of instillation of liquids used by Sewall and Powell and by Petragnani. Alexander and his co-workers make a further contribution to this problem by demonstrating the fact that some of their dander extract was found in the substance of the lung, in a certain percentage of the cases. They, as well as we in our preliminary report, have shown that animals died within from one to five minutes after inhalation of the sensitizing substance. They further refute the observations of Jones, and corroborate those of Besredka by inducing shock by intratracheal injection.

ORAL ADMINISTRATION

Before proceeding with our major experiments, we administered dry dander orally in order to eliminate the contention that, because small amounts of dander were swallowed, the digestive tract rather than the nasal mucosa might still be the portal of entry for the anaphylactogen.

Eight guinea-pigs, weighing between 280 and 420 Gm., were fed gelatin capsules (1 by 0.5 cm., containing 0.04 Gm. of dry dander). These capsules were inserted into the animals' mouths and forced past the pharynx. A little water was given to facilitate the swallowing. Occasionally an animal would begin to chew the capsule, but most of it was washed down by the water. Twenty-four such doses were given on successive days, over a period of twenty days.

Three weeks after the last oral dose had been given, intravenous injections of dander extract were made, and in none of the instances were we able to obtain any definite evidences that the animals were sensitized.

NASAL SENSITIZATION WITH HORSE SERUM

It has been amply shown by the work of Busson,[15] Sewall and Powell [27] and Petragnani [21] that the nasal mucosa can serve as a portal of entry for cattle serum, sheep or horse serum, and thus produce sensitization. It was merely as a point of contact with this past work that we did the following preliminary experiments.

25. Ratner, B.; Jackson, H. C., and Gruehl, H. L.: Nasal Sensitization, Nasal Anaphylactic Shock and Respiratory Symptoms Simulating Bronchial Asthma in the Guinea-Pig. Proc. Soc. Exper. Biol. & Med. **23**:17 (Oct.) 1925.

26. Alexander, H. L.; Becke, W. G., and Holmes, J. A.: Reactions of Sensitized Guinea Pigs to Inhaled Antigens, J. Immunol. **11**:175 (March) 1926.

27. Sewall, H., and Powell, C. (footnotes 16, 17 and 18).

In table 3, it will be noted that thirty-one drops of horse serum were instilled in each nostril of three guinea-pigs, weighing approximately 450 Gm. each. About a month later, each of these animals received 1 cc. of horse serum intravenously. Animal 337 died a typical anaphylactic death; animal 338 showed suggestive symptoms; animal 339 showed unmistakable signs of anaphylaxis, with recovery after two hours. These few results corroborate the work of former authors and need no further amplification.

SENSITIZATION INDUCED THROUGH INHALATION OF DRY HORSE DANDER

An exhaustive review of the literature discloses that no investigator succeeded in sensitizing an animal by subjecting it to the inhalation of a dry substance. Friedberger and Kamio, who have worked with dry dander, completely failed. Ulrich had attempted to sensitize animals to dry pollens, but his work is of such a fragmentary character that it is

TABLE 3.—*Guinea-Pigs Sensitized by Instilling Horse Serum into their Nostrils*

Sensitization: From 4/29/25 to 5/11/25, three animals received 1 drop of horse serum two or three times a day dropped into each nostril; on 6/2/25 and 6/3/25, each received 2 drops; total of 31 drops in each nostril, equivalent to 4.5 cc. (The animals exhaled a great deal of this each time it was dropped into the nostril.)

Date	No.	Dose	Material	Route	Results
6/26/25	337	1 cc.	Horse serum	Intravenous	Convulsions and death in 2½ minutes; lungs typical
6/26/25	338	1 cc.	Horse serum	Intravenous	Negative except for sneezing at intervals, for two hours
6/26/25	339	1 cc.	Horse serum	Intravenous	Dyspnea, marked excitement, partial collapse, recovery after two hours

unconvincing. Van Leeuwen and his co-workers sensitized animals to the spray of oats contaminated by parasites, with only a fair degree of success. Their animals showed indefinite symptoms, and they could not be regarded as those of true anaphylaxis as they appeared before a suitable incubation period had elapsed.

In October, 1925, we published a preliminary report of our work, and showed for the first time that animals could be sensitized by the inhalation of a dry substance.

Methods.—Cage: The cages used were metal boxes, about 1 by 1 by 1 foot, with a whole glass door for the front. There was a window in the top of the cage, and ventilation was obtained through several slits in the walls. No more than two or three animals were ever placed in the cage for a single experiment. A raised floor was provided for the animals. Our dry, defatted dander was deposited on the true floor of the cage.

After the dander and animals had been placed in the cage, the glass door was closed. Currents of air were then blown in by means of an ordinary hand pump attached to a tapered glass tube which was inserted into a hole in the wall of the cage below the wire floor. This produced clouds of dander in the atmosphere.

A light was placed above the glass window in the roof to afford the experimenter a clear view of the reactions and of the result of the experiments.

The narrow slits in the cage afforded ample ventilation, even for lengthy experiments, but did not permit the loss of too much dry dander.

Cotton Pledgets: Soft pieces of cotton were rolled so that they could be placed at the anterior nares. These were dipped into the dry dander and applied at the anterior nares, but were never forced into the nasal cavity. In this way we avoided the possibility of trauma which might ensue if stiff probes were used.

In the following experiments, we were able to prove definitely that sensitization by inhalations of dry horse dander can be brought about.

In table 4 is a study of a group of eleven animals, varying in size from 340 to 615 Gm., that were exposed to dry dander which was introduced into the nares on soft pledgets of cotton. The animals received from thirty-two to fifty such exposures. No attempt was made to work

TABLE 4.—*Guinea-Pigs Sensitized by Inhaling Dry Horse Dander*

Date	No.	Weight, Gm.	Dose, Cc.	Material	Route	Results
Sensitization: From 5/26/25 to 6/10/25, these animals were sensitized by being exposed to dry horse dander inhaled by placing soft pledgets of cotton containing this substance at the anterior nares; total of 32 such exposures						
7/ 7/25	355	520	1	A. E.*	Intravenous	Death
7/ 6/25	350	380	1	A. E.	Intravenous	Death in a few minutes
6/15/25	307	425	1	A. E.	Intravenous	Death in two minutes
7/14/25	366	400	1	A. E.	Intravenous	Suffusion of eyes; moderate symptoms
6/15/25	357	375	1	A. E.	Intravenous	Marked dyspnea; hind legs moderately paralyzed; recovery
7/14/25	367	400	1	A. E.	Intravenous	Marked suffusion of eyes; rapid breathing and cough; recovery
7/14/25	365	525	1	A. E.	Intravenous	Negative
6/15/25	358	615	1	A. E.	Intravenous	Slight dyspnea; negative anaphylaxis
7/ 3/25	354	430	1	A. E.	Intravenous	Moderate dyspnea; negative anaphylaxis
Sensitization: Two animals sensitized by being exposed to horse dander in the same manner from 7/14/25 to 8/3/25; total of fifty exposures						
8/24/25	405	400	1	D. E.	Intravenous	Convulsions and death
8/25/25	411	340	0.5	D. E.	Intravenous	Suffusion of eyes, heavy breathing, moderately ill; recovery

* In this and in tables 5, 7 and 10 "A. E." "D. E" refer to alkali extracts of horse dander. These extractions were made as described under methods and the letters indicate different batches of horse dander.

out the minimal number of exposures necessary, as the point at issue was to determine whether or not they could be sensitized in this manner. Further experiments will be made to clarify the question of dosage.

After a suitable incubation period, the animals were injected intravenously with 1 cc. of dander extract (table 4). The results indicate in a striking manner that sensitization can be brought about easily. Four animals (nos. 355, 350, 307, 408) died promptly in a typical anaphylactic manner; two animals (nos. 357, 367) showed marked anaphylactic symptoms with recovery; two animals (nos. 366, 411) showed definite, but moderate symptoms; three animals (nos. 365, 358, 354) showed negative symptoms. An interesting reaction in three of these animals (nos. 366, 367, 411) was that of suffusion of the eyes. This suffusion, which will be discussed later, consists at first of a watery discharge; this rapidly becomes creamy, at times almost closing the eyes, and usually disappears after from one-half to one hour.

In table 5 is shown the study of a single family of guinea-pigs. The exposure was brought about by the cage method. The pledgets of cotton used in the former experiments did not introduce any artificial factors, but the cage method employed in this experiment appears to be more nearly in accord with what happens in the natural contact of a patient with asthma.

It will be noted in table 5 that three offspring were exposed to dander, and, after an incubation period, were proved to be profoundly sensitized, since they all died in typical anaphylactic shock when they were injected intravenously with varying doses of dander extract.

One offspring, that had not been exposed to dander, received an injection of 1 cc. of dander extract intravenously without manifesting the slightest indication of anaphylaxis. The mother of this family, as well, was not exposed, and gave a negative reaction to an intravenous injection of the extract.

TABLE 5.—*A Single Family of Guinea-Pigs, Certain Members of Which Were Exposed to Dry Horse Dander and Others Not*

Date	Animal	Weight, Gm.	Age, Days	Dose, Cc.	Material	Route	Results
Sensitization: Two members not exposed to horse dander							
6/15/25	Offspring no. 1	149	3	1	A. E.	Intravenous	Negative
7/ 1/25	Mother no. 341	700	..	1	A. E.	Intravenous	Negative
Sensitization: Three remaining offspring born of mother no. 341 were exposed when they were 11 days old, to circulating dry horse dander in cages from 6/12/25 to 6/23/25 (at various intervals) for a total of 18¼ hours; eighteen days after the first exposure injections were made as noted below							
7/ 1/25	Offspring no. 2	220	30	1	A. E.	Intravenous	Death
7/ 1/25	Offspring no. 3	220	30	0.8	A. E.	Intravenous	Death
7/ 1/25	Offspring no. 4	220	30	0.5	A. E.	Intravenous	Death

We conclude, from this experiment, that the three members of the family exposed to an environment containing dander acquired a sensitization to this protein dust through inhalation, whereas the members not exposed to this environment remained normal.

ANAPHYLACTIC SHOCK AND DEATH INDUCED BY EXPOSING PREVIOUSLY SENSITIZED ANIMALS TO INHALATIONS OF DRY HORSE DANDER

As we had shown that animals can be sensitized to dry dander by nasal exposure, it was essential to take up the next phase of the mechanism to prove that animals previously sensitized to dander by parenteral injection would show anaphylactic symptoms, when brought into contact with dry dander.

For this purpose, we utilized a series of thirty-nine animals, varying in size from 250 to 700 Gm. These animals were sensitized, either by intraperitoneal or intravenous injection, the overwhelming majority

having received from 0.5 to 1 cc. of dander extract intraperitoneally. This sensitizing injection seemed to be entirely satisfactory.

The animals, on receiving the initial injection, in no instance showed evidence of natural sensitization.

After an incubation period varying from two weeks to a month or more, these animals were placed in cages and exposed to circulating dander in the manner described. The results of these experiments were so striking as to make it evident that the nasal route can serve as a

TABLE 6.—*Reactions of Sensitized Guinea-Pig Showing Marked Symptoms of Anaphylaxis from Dry Dander*

No.	Date	Weight, Gm.	Dose: Sensitizing	Dose: Anaphylactic	Route*	Results
374	7/23/25	270	1	....	Intraperitoneal	
	8/20/25	...	..	3 hr.	Cage	Collapse, marked dyspnea, suffusion of eyes, partial recovery from collapse in 15 minutes; after one hour suffusion cleared; breathing still rapid
	8/21/25	...	..	1 hr.	Cage	Marked dyspnea
	8/24/25	...	..	1 hr.	Cage	Almost immediately marked dyspnea; irritative cough; convulsive movements gradually subsiding after three-fourths of an hour; suffusion of eyes
	8/25/25	...	..	1 hr.	Cage	Dyspnea in ten minutes; rapid and jerky
	8/26/25	...	..	1 hr.	Cage	Apparently normal
	9/ 2/25	...	..	3½ hr.	Cage	Coughing, slight convulsions in five minutes; jerky breathing, coughing occasionally for about an hour; dyspnea until end of period of observation
	9/ 8/25	...	..	2 hr.	Cage	In two minutes pounding dyspnea, convulsive coughs; suffusion of right eye in ten minutes; after twenty minutes, 10 minims (1:1000) epinephrine subcutaneously; dyspnea not much lessened; suffusion disappeared
	9/15/25	...	..	2 hr.	Cage	In cage for five minutes without circulating dander, no effect; after circulating, in one minute severe convulsions; partial collapse; recovery in five minutes; suffusion of eyes lasted one hour; after recovery from collapse, heavy dyspnea; observed three hours with gradual slowing of respiration and eyes moderately suffused
	10/ 2/25	...	..	10 min.	Cage	Pounding dyspnea; coughed several times

* Cage: Animals placed in cages (with large glass windows) where they could be observed when coming in contact with the dry horse dander which was kept in circulation.

portal of entry for foreign proteins, resulting in grave anaphylactic shock and even death.

We do not give a detailed account of all these thirty-nine experiments, as the subject matter would be voluminous and would, to a great extent, be a repetition of similar results. However, it is essential that several experiments be presented in detail.

In table 6, there is an example of an animal that had been sensitized with an intraperitoneal injection of 1 cc. of dander extract. Twenty-eight days later, this animal was placed for the first time in a cage containing circulating dry dander; it showed profound anaphylactic symptoms almost immediately. The animal was placed in a cage in the same

manner on eight subsequent days. Each time, with the exception of one day when it was apparently normal, it showed the same marked anaphylactic symptoms.

Table 7 shows the effect on an animal that was sensitized previously in the same manner as that in table 6. As will be noted, when this

TABLE 7.—*Death After Sixth Exposure to Dry Horse Dander in a Previously Sensitized Guinea-Pig*

No.	Date	Weight, Gm.	Dose: Sensitizing	Dose: Anaphylactic	Route	Results
375	7/23/25	265	1 cc. D. E.	....	Intraperitoneal	
	8/20/25	...	..	3 hr.	Cage	Collapse, gasping, marked dyspnea, marked suffusion of eyes; continued for more than an hour; partial collapse lasted for two hours; animal started to recover after three and a half hours; this animal appeared almost dead during the initial collapse
	8/21/25	...	..	1 hr.	Cage	Within a few minutes, terrific pounding dyspnea; no suffusion of eyes; dyspnea continued for one hour
	8/24/25	...	..	1 hr.	Cage	Normal for one-half hour; then developed dyspnea which was milder than before; slight suffusion of eyes
	8/25/25	...	..	1 hr.	Cage	In twenty minutes rapid, jerky breathing; slight collapse; then moderate labored, jerky breathing; several spasmodic coughs
	8/26/25	...	..	1 hr.	Cage	Moderate dyspnea
	9/ 2/25	...	..	5 min.	Cage	Coughed, gasped, convulsions and death in five minutes; lungs typical

TABLE 8.—*Death After First Exposure to Dry Horse Dander in Previously Sensitized Guinea-Pigs*

No.	Date	Weight, Gm.	Dose: Sensitizing	Dose: Anaphylactic	Route	Results
389	7/24/25	300	0.5 cc.	....	Intraperitoneal	
	8/26/25	360	.....	2 min.	Cage	Convulsions and death in two minutes; lungs typical
384	7/24/25	360	0.5 cc.	.....	Intraperitoneal	
	9/ 9/25	420	.....	5 min.	Cage	After two minutes convulsions and severe coughing; collapse and death after total of five minutes; lungs typical
444	8/ 7/25	415	1 cc.	.....	Intraperitoneal	
	9/25/25	475	.....	4 min.	Cage	Convulsions, collapse and death in four minutes; lungs typical
441	8/ 7/25	475	1 cc.	.....	Intraperitoneal	
	9/28/25	500	.....	5 min.	Cage	Convulsions in three minutes; gasping markedly and death in five minutes; lungs typical, with few small hemorrhagic spots

animal was placed in the cage twenty-eight days after sensitization the symptoms induced were so profound as almost to kill the animal. The subsequent four exposures, at intervals of from one to two days, continued to produce marked anaphylactic symptoms. On the sixth exposure to dry dander the animal gasped, went into convulsions, and

died within five minutes. The lungs were typical of those found in anaphylactic death induced after intravenous injection, and there was no evidence of macroscopic dander in the trachea or bronchi.

The group of four animals in table 8 demonstrates definitely that the nasal route serves as a portal of entry for dry animal emanations. It will be noted that these four animals, of various sizes, were sensitized by the intraperitoneal route. After incubation periods of varying intervals, when they were brought into contact with dry circulating dander for the first time, they died in a typical anaphylactic manner within the strikingly short period of from two to five minutes.

With such results as these, the nasal route as a portal of entry must be accepted. How this dry substance enters the system in soluble form and acts as an anaphylactogen we cannot say. But certain it is that these animals died on coming into contact with dry dander in as short an interval as would obtain after the intravenous injection of a soluble anaphylactogen. The lungs showed typical anaphylaxis—they floated

TABLE 9.—*Results in Thirty-Nine Experiments with Sensitized Animals Placed in Cages*

No respiratory symptoms	8
Moderate but definite respiratory symptoms	15
Severe respiratory symptoms (as in table 6)	11
Death after sixth exposure (as in table 7)	1
Death after first exposure (as in table 8)	4
Total	39
Negative	8
Positive	31

in ether and were resistant to pressure—and in no instance was dry dander found in the trachea or bronchi. A summary of the results is given in table 9.

ANIMALS SENSITIZED BY INHALATION OF DRY DANDER PRESENT ANAPHYLACTIC REACTIONS RESEMBLING BRONCHIAL ASTHMA ON SUBSEQUENT EXPOSURE

We have demonstrated that animals can be sensitized by nasal inhalation of dry horse dander. We have also brought about shock and death by exposing previously sensitized animals to the inhalation of dry horse dander. In our next series of experiments we have combined these two processes in the same animal; namely, we have sensitized animals by nasal inhalation and then have induced shock in these animals by similar nasal inhalations.

In table 10 is listed a series of ten animals that were subjected to dry horse dander placed at the anterior nares with soft pledgets of cotton. These animals received a total of thirty-two such exposures over a period of fifteen days. After this exposure, the animals were

TABLE 10.—*Guinea-Pigs Not Previously Sensitized by Injection Showing Symptoms of Bronchial Asthma*

Sensitization: 5/26/25 to 6/10/25. These animals were sensitized by being exposed to dry horse dander which was inhaled by placing soft pledgets of cotton at the anterior nares, a total of thirty-two exposures

Incubation: Between 6/10/25 and 6/12/25 they received no further contact with horse dander. The incubation period, therefore, must have been between the initial exposure of 5/26/25 and 6/12/25

Later Exposures: Again exposed to dry horse dander in circulation in cages as listed below

No.	Date	Hours in Cage	Intravenous Injection	Results*
307	6/12/25	4	.....	Dyspnea and coughing
	6/13/25	1	.....	Dyspnea
	6/15/25	2	.....	Marked dyspnea and moderate collapse
	6/15/25	...	Later 1 cc. A. E.	Death in two minutes
366	6/12/25	4	.....	Marked dyspnea
	6/13/25	1	.....	Dyspnea
	6/15/25	2	.....	Dyspnea
	6/17/25	3	.....	Suffusion of one eye; dyspnea
	6/22/25	1	.....	Dyspnea and suffusion of eyes
	7/14/25	...	1 cc. A. E.	Suffusion of eyes; slight to negative anaphylaxis
	8/10/25	...	1 cc. D. E.	Death
357	6/12/25	4	.....	Dyspnea
	6/13/25	1	.....	Dyspnea
	6/15/25	2	.....	Dyspnea; lying down; sick
	6/15/25	...	Later 1 cc. A. E.	Marked dyspnea; hind legs paralyzed; gradual recovery after two hours
367	6/12/25	1½	.....	Negative
	6/13/25	1	.....	Dyspnea
	6/15/25	2	.....	Dyspnea and relaxation
	6/16/25	2	.....	Negative
	6/20/25	2	.....	Negative
	6/22/25	2	.....	Negative
	6/23/25	3	.....	Dyspnea; lay on floor
	7/14/25	...	1 cc. A. E.	Marked suffusion of eyes; extremely ill; breathing rapid; coughed several times
365	6/12/25	1	.....	Negative
	6/15/25	2	.....	Moderate dyspnea
	6/16/25	2½	.....	Negative
	6/17/25	3	.....	Negative
	6/22/25	5	.....	Negative
	7/14/25	...	1 cc. A. E.	Negative
355	6/12/25	2	.....	Dyspnea
	6/13/25	1	.....	Sneeze and coughing
	6/15/25	2	.....	Dyspnea
	6/16/25	5	.....	Dyspnea
	6/17/25	3	.....	Excitement
	7/ 7/25	...	1 cc. A. E.	Death
358	6/12/25	1½	.....	Slight dyspnea
	6/13/25	1	.....	Slight dyspnea
	6/15/25	2	.....	Moderate dyspnea and relaxation
	6/15/25	...	1 cc. A. E.	Slight dyspnea and negative anaphylaxis
	7/29/25	...	1 cc. D. E.	Death
356	6/13/25	1	.....	Negative
	6/15/25	2	.....	Slight dyspnea
	6/16/25	2½	.....	Negative
	6/17/25	3	.....	Coughed frequently
	6/22/25	5	.....	Heavy coughing and breathing
	7/ 7/25	...	Dale	Negative
350	6/12/25	1½	.....	Slight suffusion of right eye
	6/13/25	1	.....	Moderate dyspnea
	6/16/25	5	.....	Moderate dyspnea
	6/17/25	3	.....	Violent scratching, coughing, dyspnea, suffusion of right eye; exhausted, with nose in corner on dander-laden wires; coughed and sat up; cage door open for long periods of time showing no influence of lack of air
	6/20/25	2	.....	Dyspnea
	6/22/25	3½	.....	Jerky movements
	6/23/25	3¾	.....	Moderate dyspnea; lying on floor
	7/ 6/25	...	1 cc. A. E.	Death in a few minutes
354 see text				

* In all cases of death the lungs were typical of anaphylaxis.

left untreated for two days. On June 12, 1925, or seventeen days after their first exposure to dry dander, these animals were placed in cages and exposed to dander in circulation in the manner described. Throughout the period of sensitization, they showed no symptoms. However, when they were placed in cages varying degrees of dyspnea were manifested. This dyspnea is comparable in all respects to that found in a person with asthma.

Animal 307 showed definite signs of dyspnea, and, in order to prove that this dyspnea was anaphylactic, on June 15, 1925, a few minutes after the animal had shown definite evidences of collapse, it received an intravenous injection of dander extract, and promptly died in acute anaphylactic shock.

Animal 366 presented moderate signs of anaphylaxis. The symptoms manifested were dyspnea and a suffusion of the eyes. The symptoms from the last two exposures were mild, and when the animal received an intravenous injection of dander extract some time later, the response was that of moderate anaphylaxis, including suffusion of the eyes. The latter symptom, resulting after an intravenous injection, was exactly similar to the suffusion occurring when the animal was exposed to the dander, and indicates that this symptom is of an anaphylactic nature. About three weeks after the intravenous injection, a second injection was given, and the animal promptly died an anaphylactic death. This suggests that the animal became profoundly sensitized by the injection on July 14, 1925.

In animal 357, the injection produced moderate anaphylaxis with recovery, which showed that the preceding reactions—sensitization and subsequent exposures to horse dander—were those of mild anaphylaxis.

In animal 367, the same situation obtained.

In animal 365 there was an absolutely negative response to the subsequent exposure to horse dander, and also a negative response after the intravenous injection of dander extract three weeks later. This negative response throughout indicates that this animal either could not have been or was not sensitized by exposure to the dust. This experiment presents a definite problem that will be taken up later. Are there certain animals that for some reason resist nasal sensitization?

Animals 355, 358 and 350 need no further comment.

The experiment on animal 356 corresponds in all its features to that on animal 365, with the exception that the Dale method for the uterine strip test was used instead of the intravenous injection.

Animal 354, from the very inception of the attempts to sensitize it with swabs of horse dander, showed symptoms of marked dyspnea, and throughout the subsequent exposures presented similar attacks of dyspnea. These reactions were disturbing, because their early onset, long before the proper incubation period, indicated that there might have

been a natural sensitization. These fears were dispelled, however, when the animal, about a month and a half after its initial exposure, received an intravenous injection of dander extract and gave a negative response. One month later, the animal was again placed in the cage, and showed

TABLE 11.—*Guinea-Pigs not Previously Sensitized by Injection Showing Symptoms of Bronchial Asthma*

Sensitization: 8/12/25 to 8/31/25. These animals were sensitized by being exposed to dry horse dander kept in circulation in cages over a period of nineteen days, a total of 25¼ hours of exposure
Incubation: Between 9/1/25 and 10/7/25 received no further contact with dry horse dander
Later Exposures: Again exposed to dry horse dander as listed below

No.	Date	Time in Cage	Intravenous Injection	Results*
530	10/ 7/25	5 min.	.....	Severe coughing and dyspnea
	10/ 8/25	15 min.	.....	Slightly increased breathing
	10/12/25	15 min.	.....	Coughing and slight dyspnea
	10/13/25	1 hr.	.....	Marked dyspnea
	10/28/25	.....	0.1 cc. D. E.	Convulsion and death in one minute
531	10/ 7/25	5 min.	.....	Coughing and marked dyspnea
	10/ 8/25	20 min.	.....	Marked dyspnea
	10/12/25	15 min.	.....	Slight dyspnea
	10/13/25	1 hr.	.....	Marked dyspnea
	10/28/25	.....	0.5 cc. D. E.	Convulsions and death in five min.
532	10/ 7/25	5 min.	.....	Practically normal
	10/ 8/25	20 min.	.....	Slightly increased breathing; practically normal
	10/12/25	15 min.	.....	Moderate dyspnea
	10/13/25	1 hr.	.....	Normal
	10/28/25	.....	0.2 cc. D. E.	Marked dyspnea; moderate suffusion of eyes; collapse and final recovery
533	10/ 7/25	5 min.	.....	Coughing and marked dyspnea
	10/ 8/25	20 min.	.....	Practically normal
	10/12/25	15 min.	.....	Dyspnea and one sneeze
	10/13/25	1 hr.	.....	Moderate dyspnea
	10/28/25	.....	0.1 cc. D. E.	Coughing; dyspnea; moderate symptoms; final recovery
534	10/ 7/25	5 min.	.....	Dyspnea and moderate coughing
	10/ 8/25	15 min.	.....	Marked dyspnea
	10/12/25	15 min.	.....	Marked dyspnea
	10/13/25	¾ hr.	.....	Marked dyspnea
	10/28/25	.....	0.2 cc. D. E.	Convulsions and death in one min.
536	10/ 7/25	5 min.	.....	Severe coughing and dyspnea
	10/ 8/25	15 min.	.....	Normal
	10/12/25	15 min.	.....	Practically normal
	10/13/25	¾ hr.	.....	Practically normal
	10/28/25	.....	0.1 cc. D. E.	Coughing; jerky movement; collapse; convulsion; death in seven minutes
537	10/ 7/25	5 min.	.....	Dyspnea
	10/ 8/25	15 min.	.....	Marked dyspnea
	10/12/25	15 min.	.....	Marked dyspnea and severe coughs
	10/13/25	¾ hr.	.....	Marked dyspnea and suffusion of right eye
	10/28/25	.....	0.5 cc. D. E.	Immediate convulsion; terrific dyspnea; marked collapse; gradual recovery
538	10/ 7/25	5 min.	.....	Coughing and marked dyspnea
	10/ 8/25	20 min.	.....	Coughing and marked dyspnea
	10/12/25	15 min.	.....	Marked dyspnea and convulsion; cough
	10/13/25	¾ hr.	.....	Marked dyspnea; severe convulsion; jerks
	10/28/25	.....	0.5 cc. D. E.	Convulsion and death in one min.

* In all the cases of death the lungs were typically ballooned out and had all the characteristics of typical anaphylactic distention.

definite signs of anaphylaxis. The following day, the animal was found dead, and when an autopsy was performed, presented an extremely widespread pneumonic process involving both lungs, showing numerous cavities and signs of bronchial pneumonia, bilateral pleurisy and adhesive

pericarditis. These gross conditions were subsequently shown microscopically to be a nontuberculous chronic pneumonia with chronic pleurisy and pericarditis. This necropsy shows that we were probably dealing with an unusual case of chronic pneumonitis and that the dyspnea, manifested from the start, was due to the embarrassment incident to a pathologic condition in the respiratory tract. This particular experiment suggests wherein Van Leeuwen and Ulrich may have erred in those instances in which the animals presented symptoms long before the proper incubation period had elapsed.

In the experiments listed in table 11, we have some further results comparable to the preceding ones. These animals were sensitized by being placed in contact with the circulating dander which they inhaled in a natural manner. They received a total of twenty-five hours of exposure, over a period of nineteen days. They were then permitted to live in a normal environment for about five weeks. After this incubation period, they were again placed in the cages.

It will be noted from table 11 that the animals were profoundly sensitized by their exposures to horse dander, since they showed marked evidences of anaphylactic dyspnea on exposure after the incubation period. For example, animal 538 had attacks of coughing and convulsive seizures. The striking feature is that deaths were induced with as small a dose as 0.1 cc. given intravenously. These injections were used, as indicated, merely to prove that the preceding symptoms on exposure to dry dander were those of anaphylaxis.

The other facts brought out in this table need no further elucidation.

The symptoms manifested in the latter series of experiments are identical with those obtained in the ordinary anaphylactic reaction after injection. We must further concede that because these symptoms have been produced entirely through inhalation, this respiratory anaphylactic phenomenon must be identified with bronchial asthma. Further, in each one of these experiments in which we likened the condition to bronchial asthma it was in turn proved to be anaphylactic, as we were able to kill these animals with acute signs of anaphylaxis by intravenous injection of horse dander extract.

ADMINISTRATION OF EPINEPHRINE

If the foregoing experiments have demonstrated that the nasal route may serve as a portal of entry for foreign proteins, and that the symptoms of bronchial asthma may be reproduced in the guinea-pig, injections of epinephrine should alleviate the symptoms in certain animals as it does in certain patients with asthma.

We have subjected a few of our animals, in the height of anaphylactic dyspnea, to injections of epinephrine. The details of their reactions are listed in table 12.

It will be seen in this table that injections of epinephrine seemed to have some influence in lessening the marked symptoms, particularly those of dyspnea. Animal 446, which did not receive epinephrine, placed in the cage with no. 440, which had received the drug, clearly showed its influence.

Since we know that injections of epinephrine relieve smooth muscle spasm, the relief of the dyspnea in animal 440 would indicate that the

TABLE 12.—*Influence of Injections of Epinephrine During Severe Anaphylactic Reactions Induced by Contact with Dry Horse Dander*

Date	No.	Weight, Gm.	Intraperitoneal Sensitization D. E.	Time in Cage, Hours	Results
7/23/25	376	230	1 cc.		
9/15/25	...	...	....	2	After one minute with horse dander in circulation had severe convulsion and collapse lasting six minutes; developed severe dyspnea and severe convulsive coughing; dyspnea marked for about two hours; received 0.5 cc. epinephrine (1:1000) subcutaneously; ten minutes later dyspnea stopped
8/ 7/25	440	280	1 cc.		
9/25/25	...	...	....	½	Suffusion of eyes; coughing; moderate jerky convulsive movements; terrific dyspnea; furred; after ten minutes received 0.5 cc. epinephrine (1:1000) subcutaneously; great reduction of dyspnea; in about one-half hour suffusion cleared; fur smoothed out
7/24/25	388	365	5 cc.		
9/16/25	...	...	....	1	Three minutes after dander put in circulation, developed severe respirations with paroxysmal hacking cough; five minutes later animal wobbled and fell; marked dyspnea; ten minutes later received 0.5 cc. epinephrine (1:1000) subcutaneously; three minutes later dyspnea ceased; one minute later made attempts to vomit; ten minutes later eyes half closed; stretched out; showed evidence of nausea; dribbling saliva; respirations normal throughout period; observed one hour more; appeared tired
8/ 7/25	433	285	1 cc.		
9/18/25	...	...	....	1	Marked dyspnea; short convulsive movements after three minutes; no suffusion of eyes; marked pounding dyspnea for twenty minutes; then gave 0.5 cc. epinephrine (1:1000) subcutaneously; dyspnea subsided after one minute; animal became drowsy with quiet respirations; no nausea; after twenty minutes lying on side breathing easily; apparently drowsy; eyes shut
8/ 7/25	446	300	1 cc.		
9/25/25	...	...	....	½	Moderately jerky convulsions; terrific dyspnea; furred; this animal was used as a control with no. 440 (above) and was in cage at same time; while this animal remained furred with dyspnea no. 440 smoothed out and ceased dyspnea after epinephrine; contrast striking

symptoms obtained by exposure to dander were due to a spasm of the bronchial musculature, and that these phenomena are comparable to those found in bronchial asthma.

It should be remembered that the animals chosen for injections of epinephrine were those in which the symptoms were extremely profound. Had we chosen those animals in which the symptoms were much milder, the response to epinephrine might have been much more rapid and com-

plete, but our certainty as to whether a mild dyspnea had subsided or not would not have been so sharply defined.

The improvement after injections of epinephrine was slow. Referring to table 6, we have an example of an animal that received epinephrine, but was not relieved by it.

It is a common experience with those who come in contact with asthmatic subjects to find that epinephrine does not always allay the symptoms of bronchial constriction; so the situations in human beings and in animals are comparable.

COMPARISONS BETWEEN NASAL AND INTRAVENOUS DOSES

On getting certain negative responses to the inhalation of dry horse dander, in animals that had previously been sensitized, it seemed to us that possibly nasal insufflation was not always as effectual as intravenous

TABLE 13.—*Comparisons of Effects of Nasal Instillation and Intravenous Injection of Horse Dander in Sufficient Dosage to Produce Shock*

Series	No.	Nasal*	Intravenous	Series	No.	Nasal	Intravenous
1	419	—	—	16	536	+—	Death
2	414	—	—	17	456	+	Death
3	417	—	—	18	530	+	Death
4	365	—	—	19	355	+	Death
5	391	+—	+—	20	445	+	Death
6	358	+—	+—	21	413	++	Death
7	363	+	+	22	460	++	Death
8	357	+	+	23	437	++	Death
9	533	+	+	24	438	++	Death
10	537	+	++	25	538	++	Death
11	367	+—	++	26	534	++	Death
12	532	+—	++	27	531	++	Death
13	377	—	Death	28	307	++	Death
14	451	—	Death	29	350	++	Death
15	447	—	Death				

* The signs used in table 13 with their meanings are as follows: Nasal, exposures to circulating dander in cages; —, negative anaphylaxis; +—, suggestive anaphylaxis; +, positive anaphylaxis; ++, severe anaphylaxis; death, anaphylactic death.

injection in bringing about shock. It occurred to us, therefore, that it would be of great value to follow these nasal shock doses by intravenous injections. The results are tabulated in table 13.

There is, in general, a definite parallelism between the nasal and intravenous routes in their efficacy to produce anaphylactic shock, although the evidence presented in table 13 seems to be heavily in favor of the intravenous route, which is, no doubt, the best means of inducing anaphylactic shock. It must be recalled, however, by referring to tables 7 and 8, that the nasal route can, at times, produce the same anaphylactic death in as short a time as the intravenous route.

CLINICAL CONSIDERATIONS*

During the course of our studies on children with asthma, certain fortuitous and unplanned situations occurred which so closely duplicated the experiments which we have conducted with guinea-pigs that we feel they are sufficiently interesting to report.

When one of us was studying rabbit hair asthma, a number of sensitive children were brought into contact with rabbits. One of the children developed a typical attack of bronchial asthma in a few minutes. A rabbit hair, lodging in his right eye, induced marked suffusion and angioneurotic edema.

Another patient was closeted in a barn with some gardeners who were mixing seeds for the planting of a golf course. Shortly after being in contact with the dust induced by this seed mixture, the patient developed a typical and severe attack of bronchial asthma. The barn became unbearable to him, and he immediately sought relief in the open. When we learned these facts, the patient was tested with various pollen proteins. He gave positive allergic skin reactions to timothy and redtop. We then learned from the gardener that twenty-five pounds (11.3 Kg.) of redtop had been in the mixture of seeds used on the day of this incident.

Another interesting parallel to our experiments was given by Leopold and Leopold,[28] who, in a recent study on asthma, constructed a room which was absolutely dustproof. The barometric conditions in this room were so arranged as to afford perfect ventilation and obviated the possibility of extraneous conditions entering into the experiment. Patients who had been proved sensitive to certain substances were placed in this room when free from an attack of asthma. After the subject had been permitted to rest comfortably, a measured amount of the sensitizing dust was placed in the room, and within a short time he developed a typical attack of bronchial asthma.

Ancona [29] reports a study of an epidemic of asthma among millers of a certain town in Italy. This asthma was manifested toward a parasite—*Pediculoides ventricosis*—which appeared in contaminated oats, and, according to Ancona, can be acquired by any one who has had sufficient exposure to the sensitizing dust.

These clinical facts, we believe, demonstrate further that a definite relationship exists between asthma and anaphylaxis which is due to the inhalation of a foreign protein.

COMMENT

In this work we were primarily interested in ascertaining whether a state of protein sensitivity could be induced in animals through the direct inhalation of a dry animal emanation, and whether we could reproduce a symptom-complex resembling bronchial asthma. The approach to our

28. Leopold, S. S., and Leopold, C. S.: Bronchial Asthma and Allied Allergic Disorders. Preliminary Report of a Study Under Controlled Conditions of Environment, Temperature and Humidity, J. A. M. A. **84**:731 (March 7) 1925.

29. Ancona, G.: Asma epidemico da Pediculoides Ventricosis, Policlinico (sez. med.) **30**:45, 1925.

problem was difficult, because we had to deal with an animal substance that could serve as an anaphylactogen both in the dry and liquid states.

Independent of work done by Coca, Longcope and their respective co-workers, on the anaphylactogenic properties of horse dander, we, too, refuted the assertion of Friedberger and Kamio that horse dander was not an anaphylactogen. Having demonstrated that these anaphylactogenic properties are inherent, we were able to proceed with the problem of inducing a state of sensitization by natural contact with this dry dander.

In the previous work on this subject, none of the investigators attempted to produce this mechanism under conditions closely enough resembling those found in the human subject. For example, the major part of the work done by others was with the installation or spraying of serums or of liquid extracts, as will be found in the work of Friedberger, Busson, Sewall and Powell, Petragnani, Friedberger and Kamio, Busson and Ogata, and Alexander, Becke and Holmes.

Friedberger and Kamio were the first to attempt this mechanism with a dry animal emanation, but unfortunately they were unsuccessful in producing the desired results, and concluded, therefore, that there was no relationship between human idiosyncrasy and anaphylaxis.

Ulrich, working with pollens, claims to have sensitized and produced shock in his guinea-pigs successfully by the inhalation of these pollens. His work, preliminary report, in 1918, gives but a meager number of experiments, which have not been enlarged on since that time. The criteria for anaphylaxis in these few experiments are not amply justified, since he considered positive reactions to have occurred within five or six days after the first contact, disregarding entirely the requisite incubation period. These facts alone make the entire work seem unconvincing.

Van Leeuwen, quoting some unpublished work that he did in collaboration with Landsteiner, states that they were unable to produce shock in previously sensitized animals by the inhalation of pollens and dried horse serum.

Van Leeuwen, Bien and Varekamp attempted to sensitize animals nasally with oat grain contaminated by parasites. In their experiments, symptoms were manifested within a shorter time than the incubation period necessary for sensitization and for the most part they were the irritative symptoms of the upper respiratory tract. These facts suggest that these investigators have been working with a substance manifesting a primary toxicity and not with a true anaphylactogen. This point of view the authors themselves suggest. They further suggest that this substance is an "asthmogen" and not a true anaphylactogen. Their guinea-pigs, further, show a rise in temperature which is contrary to the accepted idea that in anaphylaxis there is a fall in temperature, and their autopsy observations do not coincide with what we regard as anaphylactic lungs.

In our work, we have adhered strictly to the use of a dried dander powder which was devoid of fat and in no way changed metabolically. It might be argued that our dander is different from the dander inhaled by a person in a natural contact. However, in a series of experiments, we have shown that the fat extracted from the dander was nonanaphylactogenic, so that nothing of any value is taken away by this extraction. It seems that in removing the fat and heavier particles we were actually removing substances that are the result of an intensive combing, and that therefore we are here dealing with a dander that might be more nearly comparable to that with which one might naturally come in contact.

It should further be noted, from reference to our protocols, that the environment in which the guinea-pigs were placed was as natural as that of a human being.

By successive stages in our experiments, we have sensitized animals through the inhalation of dry horse dander, and we have produced shock and even killed previously sensitized animals by the inhalation of this substance. Finally, we have also combined the first and second phases of this mechanism in the same animal, and have reproduced a symptom-complex resembling bronchial asthma in the human being.

Alexander, Becke and Holmes quote an article published by Sewall in 1914, and state that he distinguished the symptoms of anaphylaxis due to the spraying of serum from those of bronchial asthma. However, if these authors will refer to an article published by Sewall in 1917, entitled "Experimental Asthma in the Guinea-Pig" they will note that "it has been shown that guinea-pigs, especially after sensitization, may react to intranasal instillation of horse serum by the development of respiratory seizures which have the essential characters of bronchial asthma." Alexander, Becke and Holmes conclude that "the symptoms manifested in those guinea-pigs that responded to the sprayed extract were typically anaphylactic in character and resembled asthma no more than when antigens are introduced into these sensitized animals by other routes."

In as high regard as we hold the excellent work of Alexander and his co-workers, we believe that the hypothesis of Sewall, that these symptoms are essentially those of bronchial asthma, is the correct one. It is our contention that the anaphylactic symptoms demonstrated in the animals of Sewall, Petragnani, Busson and Ogata, and Alexander, Becke and Holmes, as the result of the instillation and spraying of liquid antigens, do resemble the symptoms manifested in a person with asthma.

However, none of these investigators have satisfied all the requirements for this assumption as we have been able to do, particularly by using a dry antigen and by carrying out both sensitization and shock in the same animal through the natural inhalation of a dry substance. Our

animals might, therefore, be placed in the same category as an asthmatic patient who, one might reasonably contend, did not receive a previous injection.

We did not experiment directly with human subjects, but we have been fortunate in having our experiments accidentally duplicated in their entirety, as shown by the incidents narrated in our clinical considerations.

Further, in our experiments, the action of epinephrine was similar to that in the human being with asthma. The influence of epinephrine that we have found is contrary to the results obtained by Piazzi,[30] who finds that epinephrine and atropine do not exert so favorable an influence in animal anaphylaxis as they do in asthma.

The exact point at which foreign substances enter the respiratory tract is under much discussion.

Sternberg discusses this problem at great length, and suggests that Petragnani was the first to delimit definitely this absorption at the point of the nasopharynx, and that Busson, Sewall and the others made no attempt at this delimitation. Besredka apparently ignores the question of nasopharyngeal absorption, as he worked exclusively with intratracheal injection, and feels strongly that the trachea is the portal of absorption for foreign particles. Sternberg and Alexander and his co-workers demonstrate the presence of the inhaled foreign substances in the alveoli of the lung.

Blumgart [31] summarizes his interesting work by stating that the nasopharynx constitutes an area of singular absorption and that crystalloids, colloids and, to a lesser extent, inert substances traverse the nasopharyngeal mucous membrane by being absorbed by way of the olfactory nerve cells and thence to the systemic lymphatics.

Petragnani, we—in our preliminary report—and later Alexander and his co-workers showed that death occurred through the induction of acute anaphylaxis in the surprisingly short period of from one to two minutes after inhalation. The rapidity with which these substances must have entered the system was directly comparable to that of an intravenous injection (Besredka made similar claims for intratracheal absorption).

The work of others, demonstrating the absorption of liquid substances, were striking enough in themselves, but our demonstration of the absorption of a dry antigen, which presumably had first to be put into solution by the nasal mucosa before it could enter the system as a soluble antigen, lends further proof to the hypothesis that dry antigens as well as colloidal antigens may traverse the upper respiratory tract.

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30. Piazzi: Ann. clin. med., vol. 7, 1916, quoted by Friedberger and Kamio (footnote 3).

31. Blumgart, H. L.: A Study of the Mechanism of Absorption of Substances from the Nasopharynx, Arch. Int. Med. **33**:415 (April) 1924.

For the present, we might assume that the absorption from the oral administration of dry horse dander does not play any rôle in this particular type of "respiratory anaphylaxis." This is in accord with the work of Sewall and Powell, published in 1916.

Whether asthma, in all instances, is an acquired disease, or whether it is hereditary, cannot be answered in its finality with the meager evidence which we have at present. That a certain predisposition to the development of this disease is essential, one must accept both in the animal and in the human subject. What we are mainly concerned with, however, is that, given a predisposition, one can, by governed factors, acquire bronchial asthma or "respiratory anaphylaxis."

Rackemann,[32] in putting the question "Can hypersensitiveness be acquired?" presents certain clinical circumstantial evidence for this theory which, in the main, is similar to what we presented prior to his, in our work on "Rabbit Hair Asthma," and which such workers as Ancona, Schloss and others have presented at other times. Rackemann asks for some direct evidence in support of his theory. We believe that we have given such evidence in our protocols.

We believe that the evidence presented in this paper strongly emphasizes the theory that the problem of idiosyncrasy or allergy in the human subject and that of anaphylaxis in the animal are closely related.

SUMMARY AND CONCLUSIONS

1. Horse dander, when used in the dry state or in solution, can serve as an anaphylactogen.

2. A method is presented for the preparation of dry dander, and tor the extraction of an anaphylactogen from this substance.

3. Guinea-pigs have been successfully sensitized by the inhalation of dry horse dander.

4. Shock has been induced by the inhalation of dry horse dander in guinea-pigs previously sensitized by the injection of dander extract, and they have even been killed.

5. Guinea-pigs, sensitized by the inhalation of dry horse dander, when again subjected to the inhalation of dry horse dander after a suitable incubation period, showed respiratory symptoms of anaphylaxis.

6. The symptoms noted in the last group are not different from those observed in the human being with asthma.

7. Epinephrine alleviates the symptoms in the latter group in the same manner in which epinephrine affects human beings suffering from an attack of asthma.

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32. Rackemann, F. M.: Can Hypersensitiveness Be Acquired? J. A. M. A. **84**:489 (Feb. 14) 1925.

8. The nasal route can, if conditions are proper, serve as a portal of entry for foreign proteins, in the dry or liquid state, in the same way that a parenteral injection can do so.

9. We believe that foreign proteins may enter the circulation through the nasopharynx; this is based on the fact that death occurred after nasal inhalation almost as soon as after an intravenous injection.

10. The swallowing of dry dander in capsules does not sensitize animals.

11. A state of anaphylaxis was produced in the guinea-pig under conditions that would be regarded as natural, i. e., without the introduction of a substance by direct injection, and therefore supports the theory of "acquired sensitization in the human being."

12. The experimental data in the animal and clinical evidence in the human being are shown to be so closely related as to suggest the point of view that anaphylaxis in the animal and asthma in the human subject are fundamentally the same.

13. This particular type of anaphylaxis induced in the guinea-pig by the inhalation of a dry animal emanation we should like to call "respiratory anaphylaxis" as opposed to anaphylaxis induced by parenteral injections.

THE RELATION OF MATERNAL DIET TO HEMORRHAGE IN THE NEW-BORN*

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The etiology of hemorrhage in the new-born, except in cases of hemorrhagic disease, is one of the puzzling problems of medicine. Whenever such hemorrhage occurs, trauma or syphilis is suspected, but frequently autopsy does not reveal either of these. In animals such causes are eliminated *a priori*. Hence, on discovering cerebral hemorrhage in young rats, it seemed expedient to make a biologic study of this subject.

In our laboratory it has been found that certain synthetic diets containing a limited amount of vitamin B apparently are associated with hemorrhage, whereas stock diets are not. Female rats fed from the time of weaning on the minimum amount of vitamin B necessary for normal growth and conception, are unable usually to deliver and carry their young through the lactation period. None of the mothers have shown signs of avitaminosis unless excessive hemorrhage at delivery is considered an indication of this condition. Although a rat normally delivers her young without visible loss of blood, a number of mothers on this diet have died from hemorrhage, and many others have soaked their bedding during parturition.

The ultimate penalty of an inadequate maternal diet, however, is vicariously paid by the young. With limited vitamin B in the food of the mothers, one of three conditions results: (1) abortions or absorptions of the embryos, (2) death of the young at birth or (3) death during the nursing period. The deaths occurring at birth or during the first few days of life are characterized by hemorrhages varying in volume and location; a certain number of those occurring during the second week exhibit, in addition, marked emaciation, gastric stasis and myelin degeneration of the vagus and phrenic nerves. Occasionally, after the first stage of paralysis has developed, one or two out of a litter are strong enough to eat from the mother's ration, and these usually recover.

The majority of deaths occur at approximately twenty-one days, when weaning should normally take place. For a day or two before their

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deaths, these animals exhibit distinct symptoms of advanced beriberi, such as a loss of muscular coordination, dragging of the hind limbs and, occasionally, convulsions. Death comes on rapidly, and autopsy reveals any or all of the following conditions: enlarged right ventricle, and small hemorrhages in the lungs, liver, myocardium, thymus, brain or other parts of the body. The vagus, sciatic and other myelinated nerves show advanced myelin degeneration.

The exact mechanism of this hemorrhagic condition is still in doubt. There is a possibility of a vasomotor derangement comparable to that associated with the now familiar degenerations in myelinated nerves; or the pathologic condition may be found in the endothelium itself. Further experimental work is being carried out along this line.

Among the problems involved are: 1. For how long a time previous to delivery should a female have an increased amount of vitamin B? 2. How much greater is the vitamin requirement during pregnancy and lactation than that necessary simply for growth and apparent adult health? Concerning the first problem we have as yet no conclusive evidence, although a series of experiments is now under way which we hope will furnish the necessary data.

The amount of vitamin B needed in the diet of experimental animals to prevent avitaminosis in their nursing young is practically four times the amount apparently adequate for the normal growth and well-being of the mother. When such an increase is made (in the form of desiccated yeast) the majority of the young are weaned at the normal age and weight, and they in turn produce healthy young to the third and fourth generations.

Occasionally a litter, or several animals from a litter, show the hemorrhagic condition or the paralysis and mild myelin degeneration even when on this increased amount of vitamin B, but this is the exception rather than the rule. These observations have led us to believe that even this level of vitamin B is near the borderline of the requirement for successful lactation or that perhaps the mammary threshold for vitamin B varies with the individual and in some cases is exceptionally high.

Most investigators agree that rats do not normally require vitamin C, the antiscorbutic vitamin, for growth and well-being. However, to eliminate the possibility of vitamin C being an etiologic factor in the hemorrhagic condition found, an investigation was made in which the rats received the regular basal diet containing 2 per cent yeast and, in addition, 10 per cent lemon juice as a drink when desired. These animals did not show any appreciable decrease either in the number of cases of hemorrhage in the young or in the number which died later of paralysis. As stated before, an increase of vitamin B in the diet practically eliminated both of these conditions.

After thus producing hemorrhage experimentally in our animals, almost at will, our next step was to record carefully the maternal diets in cases of intracranial hemorrhage and melena neonatorum in human beings, particularly in cases without an easily ascertainable cause. In our cases of hemorrhage in the new-born, the patients have routinely been treated by lumbar puncture and injection of blood, 50 cc. per kilogram of body weight being given subcutaneously in a single dose. Recovery is so usual that the child forming the basis of this report is the first one on which an autopsy could be held so as to connect definitely animal research with clinical experience.

This case occurred in the new-born pediatric service at the Multnomah County Hospital. The baby was born at home, but on account of the mother's severe hemorrhage, both mother and child were immediately transferred to the hospital. With the assistance of the intern, Dr. Arthur Harris, the nurses and the dietitian, we were able to make a rather complete study. The Portland Free Dispensary kindly placed its obstetric records at our disposal.

REPORT OF CASE

History and Diet of the Family.—The mother was a multipara, aged 36, who had had seven previous normal deliveries. All the children were living and well except one child who died of pneumonia at 2 years of age, and another who was drowned at the age of 8, two days before the present delivery. The nervous shock to the mother at this time might be considered as causing labor prematurely, were it not that the gestation period and the baby's weight were within normal limits.

The family had formerly lived on a small farm, but had moved into the city eight months before the birth of the baby. The income averaged $50 a month, $15 of which went for rent, leaving $35 for food and clothing for eight persons. The oldest child was 14 years old, and the youngest 2 years. The house was clean, the mother intelligent and cooperative. The mother believed that the best economy was to provide concentrated food for the family. The diet, therefore, consisted largely of starches in the form of white rice, rolled oats, potatoes and white bread. About twice a week they had a little boiled meat or hamburger, some stewed fruit and a few carrots or cabbage, but as there was never enough vegetables for all, the mother unselfishly deprived herself and, inadvertently, her unborn child of these vitamin-containing foods. From the daily quart of milk the mother used only about a tablespoonful in her tea. They never had butter, eggs, fish, succulent vegetables, fresh fruits, whole grain cereals or whole wheat bread.

Pregnancy and Labor Record.—The nausea of early pregnancy was severe, although the mother managed to do the housework for the family. She felt miserable and "fagged out" during the whole nine months of the pregnancy. She had little appetite for the food obtainable, but craved meat and various kinds of greens. During the ninth month she vomited after almost every meal. Records of the physical examination state that at the time of delivery she was "somewhat pallid and undernourished." Her normal weight during the preceding four years had been about 205 pounds (93 Kg.); her weight before delivery was 180 pounds (81.6 Kg.).

The baby was born 269 days after the beginning of the last menstruation. The first stage of labor took one hour and fifty minutes, resulting in complete dilatation; the second stage, ten minutes, with a spontaneous delivery; left

occipital anterior position; there were no lacerations. Obstetric anesthesia with ether was continued for five minutes. The third stage required twenty minutes. There was spontaneous expulsion of the placenta intact. Hemorrhage was marked, the patient losing about 1,000 cc. of blood before being removed to the hospital. Ergot was administered by mouth.

History and Physical Examination of the Infant.—Baby P., a girl, birth weight 3,390 Gm. (7½ pounds), was plump, well nourished and normally active. During the first four days her loss in weight was 400 Gm. (14 ounces), in spite of receiving breast milk from another source during her own mother's three day prelactation period. On the third day a slight jaundice of the skin appeared, which later deepened and extended to the sclerae. On the fourth day the borders of the heart were within normal limits, the transverse diameter being 1.5 by 3.5 cm. The pulse rate was 196. The liver was palpable 3 centimeters below the costal margin in the right mammary line. A mass could be felt in the lower left quadrant of the abdomen. Respirations were 60 a minute. The mucous membranes were pale, and the extremities cold to the touch. The stools were loose, green and mucoid. From the third to the fifth day the urine napkins were blood-tinged, and at times pinhead-sized clots were seen.

On the fifth day the baby began to vomit, and its abdomen became distended. The temperature, which had been normal, jumped to 103.2 F. (39.5 C.), then slowly dropped. The baby died that night, gasping for breath.

Observations on the blood on the third day were as follows: hemoglobin (Sahli), 92 per cent; erythrocytes, 3,552,000; leukocytes, 18,500; polymorphonuclears, 81 per cent; clotting time, eighteen minutes; bleeding time, ten minutes; sedimentation time, 24 mm. in eighteen minutes. The Wassermann reaction was negative.

Treatment.—The urinary hemorrhages were considered due to an avitaminosis. Instead of following our usual routine of giving a massive single injection of blood, we decided to try giving vitamins in comparatively large quantities by mouth. The child therefore received daily one tablespoon of orange juice and one tablet (0.5 Gm.) of yeast. Within thirty hours distinct clinical improvement was noted, especially when the child was at the breast. However, the treatment given did not prevent a fatal outcome.

Autopsy.—The following is taken from the autopsy record as made by the pathology department of the University of Oregon Medical School twelve hours after death: "The skin has a yellowish hue, but shows no signs of disease or injury. The subcutaneous fat in the usual midline incision is about 4 mm. in thickness and is the characteristic greyish yellow. When the chest was opened, both lungs were found to lie free in the pleural cavities and presented no noteworthy gross changes. The right side of the heart is markedly dilated and hypertrophied.

"In the abdominal cavity a large amount of fluid and clotted blood is seen extending between the diaphragm and right lobe of the liver and dissecting extensively extraperitoneally. Ruptured subcapsular hemorrhages of the right kidney and right suprarenal seem to be the points of origin of the extravasated blood, and the upper pole of the right kidney and the left kidney as a whole show on gross section numerous subcapsular, cortical and medullary hemorrhages.

"When the stomach was opened the mucosa was found intact. In the pyloric region of the stomach and extending down the duodenum for a distance of 4 cm. there is seen a marked hyperemia. The mucosa of the bladder presents numerous patches of hemorrhage. An autopsy was not obtained on the brain and spinal cord, but several nerves of the lumbar plexus were removed for microscopic study.

"*Anatomic Diagnosis.*—Ruptured subcapsular hemorrhages of the right suprarenal and right kidney with dissecting extraperitoneal hemorrhage; extensive subcapsular, cortical and medullary hemorrhages of the left kidney; dilatation and hypertrophy of the right ventricle of the heart; hyperemia of the stomach

and duodenal mucosa; petechial hemorrhages in the mucosa of the urinary bladder and generalized icterus were found.

"*Microscopic Examination.*—The spleen shows well formed malpighian corpuscles and a normal looking stroma. There are numerous cells loaded with hemosiderin and an abundance of this pigment is scattered loosely throughout the tissue. The walls of the blood vessel appear healthy and intact, and all types of blood cells are to be seen.

"The liver cells show to a great degree cloudy swelling and vacuolization of both the small and large globular type (fig. 1). There are numerous areas of focal necrosis scattered irregularly through the section with no relation to the hepatic lobule. An enormous amount of hemosiderin is deposited throughout or

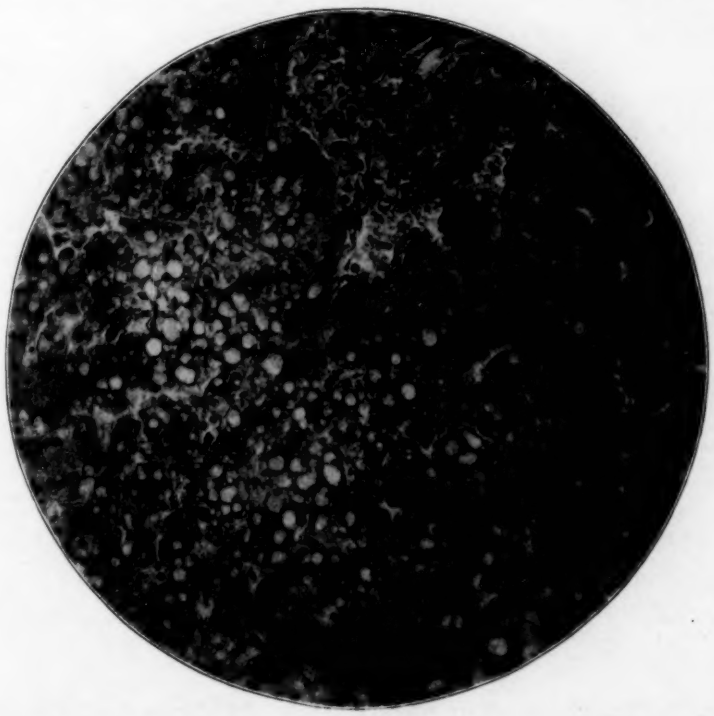

Fig. 1.—Photomicrograph of a section through the liver of a new-born infant that died of beriberi and extraperitoneal hemorrhage. Note the extensive vacuolization and deposit of pigment.

is still contained in phagocytic cells. In certain places an extravasation of red cells into the tissue spaces has occurred.

"The lungs show no abnormality nor consolidation.

"The section of intestine seems to be from the lower duodenum and is the normal expected in a new-born child. There is a slight sloughing of the epithelium in parts, but this is possibly an artefact.

"The kidney shows multiple, circumscribed, focal hemorrhages in both the cortex and medulla, with a tendency to radial dissection toward the pelvis (fig. 2). The region most involved is between the collecting tubules. The cells of the latter show parenchymatous degeneration and in some areas a slight desquamation. The glomeruli are least injured, although engorged with blood.

"The musculature of the bladder shows some vacuolization and cloudy swelling, and this section is practically denuded of epithelium.

"The stroma of the thymus shows little change, but Hassall's corpuscles, although numerous, are in all stages of decomposition.

"The tissue of the suprarenal was badly torn by the hemorrhage, and only a few characteristic cells could be found.

"No pathologic change is present in the heart unless minor changes are masked by postmortem decomposition which resulted from an unavoidable delay in the fixation of this specimen."

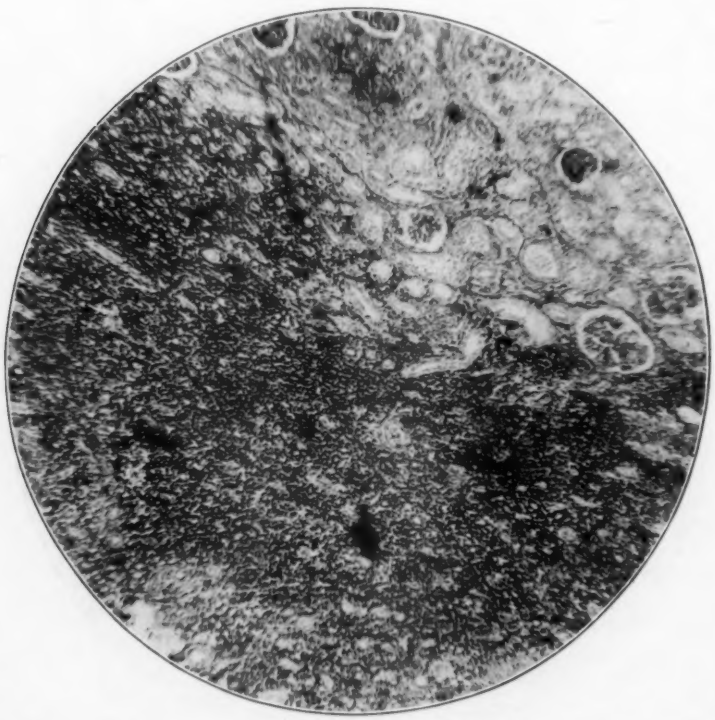

Fig. 2.—Photomicrograph of a section through the kidney of same patient as shown in figure 1. The large amount of cortical hemorrhage is remarkable.

A number of nerves taken from the lumbar plexus, when stained with osmic acid showed undoubted myelin degeneration, from the early to the more advanced stages. These neurologic observations were corroborated by Dr. William F. Allen, head of the Department of Anatomy, University of Oregon Medical School.

COMMENT

This case of hemorrhage in the new-born presents the pathologic evidences of beriberi. We assume that, in the absence of other demonstrable causes, the factor producing the beriberi is etiologically related to the hemorrhage.

Since similar signs and symptoms, together with gross and microscopic necropsy observations, have been found in experimental animals, and since these conditions can be reproduced repeatedly on a synthetic diet containing a limited amount of vitamin B, we are led to believe that the chief cause of hemorrhage in this infant was the deficiency of its mother's diet in respect to this vitamin.

The diet of the human mother was lacking also in the antiscorbutic vitamin, but the child showed neither the clinical syndrome nor the necropsy observations of scurvy, and, although antiscorbutic treatment was instituted, the usual rapid relief did not follow. In the light of the experimental work and in the presence of myelin degeneration, so typical of a deficiency of the antipolyneuritic vitamin, we do not feel that it is necessary to postulate a second deficiency to explain the hemorrhagic condition, although we recognize that it is probably present.

It is altogether possible that if an injection of blood in the usual amount of 50 cc. per kilogram of body weight had been given on the third day, when bloody urine was first noted, it might have saved this baby. The blood would have provided at once vitamins, minerals, hemostatics and other necessary factors. At any rate, vitamins given by the digestive tract were inadequate, were given too late or were absorbed too slowly.

Whether or not beriberi is a common cause of hemorrhage in the new-born cannot be decided until there are additional reports. Some of the maternal diets now resorted to for the purpose of producing small babies may be the unsuspected cause of certain pathologic conditions. Diets restricted by poverty, pernicious vomiting, diabetes or other causes need careful scrutiny from the standpoint of vitamins.

SUMMARY

Avitaminosis as a cause of hemorrhage of the new-born has been demonstrated on experimental animals. A human case coming to autopsy showed similar gross and microscopic observations, without evidence of disease in the hematopoietic system.

The mother's prenatal diet was markedly deficient in the water-soluble vitamin B. Abnormally profuse hemorrhage occurred during a precipitate delivery.

The baby did not show contusions or other external abnormalities at birth. The symptoms which developed were rapid pulse and respiration, cold extremities, hematuria, jaundice and diarrhea.

The postmortem observations demonstrated hypertrophy and dilatation of the right ventricle; hemorrhage from the right suprarenal and kidney with extensive retroperitoneal dissection; cortical and medullary hemorrhage of the left kidney; cloudy swelling and vacuolization of the liver with deposition of pigment; hyperemia of the stomach and duodenum near the pylorus and the myelin degeneration of certain nerves as found in beriberi.

MALIGNANT NEUROBLASTOMA

REPORT OF THREE CASES *

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Wahl,[1] in his paper on neuroblastoma in 1914, stated that it was possible to recognize this particular tumor much more readily than previously. This advance he attributed to the extensive investigation of the development of the sympathetic nervous system. The number of cases reported has increased considerably during the last few years; the literature contains detailed and exhaustive studies of the development of the sympathetic system, as well as descriptions of the macroscopic and histologic appearance of tumors which affect it. We believe, however, that the present report is justified because of the comparative rarity of the tumor under discussion.

The diagnosis of "malignant neuroblastoma" is seldom made clinically. If we study the histories and records of the reported cases, as well as those of our own, we usually find the antemortem diagnosis of "sarcoma of the kidney" or "sarcoma of the liver." Pepper [2] and Hutchinson [3] have described two distinct clinical types. The former spoke of a rapid and progressive distention of the abdomen without ascites, with jaundice (not in all cases), pain, fever and enlargement of the liver. He cites cases reported by Heaton, Orr, Parker and De Ruyter, as well as several of his own observations. Hutchinson [3] gives a clinical syndrome of ecchymosis over one eyelid, unilateral exophthalmos, tumefaction of the temporal region and enlargement of the regional lymph nodes. This clinical manifestation is caused by metastasis from the suprarenal tumor to the calvarium, ribs, spine or other bones. The liver, kidneys and abdominal lymph glands may be affected.

The undifferentiated malignant neuroblastoma arising in the abdominal sympathetic system or in the medulla of the suprarenal can be traced back genetically to the sympathetic formative cells, the "Bildungszellen"

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* From the Department of the Laboratories and the Department of Pediatrics, New York Post-Graduate Medical School and Hospital.

1. Wahl, H. R.: Neuroblastoma, with the Study of a Case Illustrating the Three Types that Arise from the Sympathetic System, J. M. Research **30**:205, 1914.

2. Pepper, W.: A Study of Congenital Sarcoma of the Liver and Suprarenal, Am. J. M. Sc. **121**:287, 1901.

3. Hutchinson, R.: Suprarenal Sarcoma in Children with Metastases into the Skull, Quart. J. Med. **1**:33, 1907.

of Wiesel.[4] The latter demonstrated in his papers on the development of the suprarenal that at a certain stage these formative cells descend and penetrate the epithelial anlage of the suprarenal, where they place themselves in rosette-like formation around the so-called "Markballen," the medullary bales or bundles. Of the greatest importance for the understanding of these tumors is Wiesel's further exposition of the fact that with cessation of embryonal life the evolution of the suprarenal medulla is not necessarily completed. Even beyond puberty the medulla contains formative cells or neuroblasts. This explains why neuroblastomas are most frequently found in the suprarenal medulla. However, it may be assumed that postembryonal inclusions or detachments of neuroblasts (primitive nerve cells) may occur elsewhere in the body, wherever nerve tissue, mainly sympathetic, is located. Several cases of extrasuprarenal neuroblastic tumors are reported.

Sympathetic neuroblasts differentiate into ganglion cells and chromaffin cells. Accordingly, we differentiate three types of tumor: neuroblastoma, ganglioneuroma and chromaffinoma. The first named is the most malignant, as it grows rapidly and is fatal within a short time. The other two tumors are highly differentiated, more mature, grow more slowly and are relatively benign. The first to recognize the true nature of the neuroblastoma was Marchand,[5] who noted that the cells in the tumor in his case resembled the ones found in the medulla of the fetal suprarenal. Küster [6] described two cases of tumors which he interpreted as gliomas. Wiesel,[7] in discussing Küster's paper, referred to his own previous work on the development of the suprarenal medulla, and maintained that these tumors were of nervous origin.

Since Marchand's first description and Küster and Wiesel's controversy, several similar tumors have been described. Part of these have been designated as neuroblastomas, and others have been classed as gliomas. Examples of these are the cases of Amberg, Lapointe and Lecéne,[8] Alezais and Imbert,[9] Wahl,[1] Hecht, Schilder,[10] Pepper,[2] and

4. Wiesel, J.: Beiträge zur Anatomie und Entwicklung der menschlichen Nebennieren, Anat. Heftel. **19**:481, 1902.

5. Marchand: Beiträge zur Kenntnis der glandula carotica und der Nebennieren, Festschrift f. R. Virchow **1**:578, 1891.

6. Küster, H.: Ueber Gliome der Nebennieren, Virchows Arch. f. path. Anat. **180**:117, 1905.

7. Wiesel, J.: Bemerkungen zur Arbeit H. Küsters "Ueber Gliome der Nebennieren," Virchows Arch. f. path. Anat. **180**:553, 1905.

8. Lapointe et Lecène: Gliome primitive de la capsule suprarénale, Arch. de méd. expér. et d'anat. path. **19**:69, 1907.

9. Alezais et Imbert: Tumeur précoccygienne de nature vraisemblablement parasympathétique, Compt. rend. Soc. de biol. **42**:971, 1907.

10. Schilder, P.: Ueber das maligne Gliom des sympathischen Nervensystems, Frankfurt. Ztschr. f. Path. **3**:317, 1912.

Hutchinson.[3] Wright,[11] in a study and case report, confirmed the opinion of Wiesel and Marchand, and demonstrated that the cells of the tumor were embryonal nerve cells or neuroblasts. The fibrils associated with these cells did not take the neuroglia stain or the collagen stain of Mallory. In this respect they showed a behavior identical with that of the fibers of the primitive nerve cell. The tumor cells and their fibrils were found to resemble the Bildungszellen-like and Markballen-like arrangement of the embryonal sympathetic anlage cells and that of the embryonal suprarenal medulla.

Following Wright's simple and clear exposition of the matter in his paper of 1910, numerous tumors which had previously been reported as sarcoma of the liver or kidney were reclassified as neuroblastomas of suprarenal or extrasuprarenal origin. The subsequent literature contains not infrequent reports of tumors of this nature. Among the best reviews are the papers of Wahl [1] and Lehman.[12] Cases have also been described by Ritter,[13] Anderson and Shennan,[14] Boyd,[15] Lederer [16] and others.

REPORTS OF AUTHORS' CASES

CASE 1.—A. O., a girl, aged 19 months, was admitted to the babies' ward on Nov. 22, 1924, with a swelling of the abdomen which had been increasing for two weeks, accompanied by vomiting which at first had occurred daily but which had become more frequent later. For three days there had been marked anorexia and malaise, with dyspnea. Other cardiac or respiratory and urinary symptoms were not observed. The past and family histories were negative.

Physical examination showed a pale infant with a tense, distended abdomen, exhibiting moderate dyspnea, but not appearing acutely ill. The head, neck, heart and lungs were normal. Glands were not palpable. In the left upper quadrant was a firm, immovable, rounded mass extending to the umbilicus. Over this, several enlarged and tender glands could be felt at the costal margin. Rectal examination revealed the presence of other masses on the posterior rectal wall, apparently enlarged nodes. A diagnosis of malignant neoplasm was made at this time.

The blood count showed: red cells, 2,832,000; hemoglobin, 39 per cent. (Sahli); white cells, 5,000; polymorphonuclears, 66 per cent, small lymphocytes, 32 per cent. Chemical analysis of the blood showed a uric acid content of 8.5 mg. per hundred cubic centimeters; urea nitrogen, 9 mg. per hundred cubic centimeters; sugar, 0.084 per cent; cholesterol, 0.111 per cent; chlorides, 0.563 per cent; serum albumin, 4.43 per cent; globulin, 2.44 per cent; total serum proteins, 6.87 per cent. The urine had a specific gravity of 1.028, a heavy trace of protein, a faint trace of sugar and a few white cells. The Wassermann reaction was negative. A

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11. Wright, J. H.: Neurocytoma or Neuroblastoma, a Kind of Tumor not Generally Recognized, J. Exper. Med. **12**:556, 1910.

12. Lehman, E. P.: Neuroblastoma, with Report of a Case, J. M. Research. **31**:309, 1917.

13. Ritter, S. H.: Neuroblastoma of the Intestine, Am. J. Path. **1**:519, 1925.

14. Anderson and Shennan: A Neuroblastoma of the Thoracic Cavity, J. Path. & Bact. **26**:546, 1923.

15. Boyd, W.: Three Tumors Arising from Neuroblasts, Arch. Surg. **12**:1031 (May) 1926.

16. Lederer, M.: Neuroblastoma Malignum, J. Cancer Research **10**:377, 1926.

roentgenogram of the abdomen showed a shadow in the left upper quadrant, due to tumefaction of the kidney.

An exploratory laparotomy performed on Dec. 4, 1924, disclosed a large tumor mass involving the left kidney, with extensive metastases. A section was made of the tumor mass for pathologic study. A transfusion was performed, and stimulants were given, but the child died on the following day.

Autopsy was performed six hours after death. The permission unfortunately limited the examination to the site of the operative incision and the removal of the tumor. As far as we could determine from an examination of the abdominal cavity, the tumor occupied the left upper quadrant and extended down to about 3 cm. below the umbilicus in the midline. It was retroperitoneal, the peritoneum being broken through by the biopsy incision and in some places invaded by the tumor mass. The whole abdominal cavity was filled with extensive metastatic tumors, necrotic and hemorrhagic in appearance. There were numerous enlarged lymph nodes along the aorta and the iliac vessels of the pelvis. The mesenteric

Fig. 1 (case 1).—Tumor originating in suprarenal medulla. The kidney was depressed, but not involved by the tumor mass.

folds showed invasion by tumor tissue with hemorrhage and necrosis. The liver, right kidney, spleen and pancreas did not show any gross changes on inspection or palpation.

Examination of the tumor showed the kidney to be of normal size and shape except at the upper pole, where the neoplastic growth depressed the normal contour to a depth of from 6 to 7 mm. Part of the suprarenal cortex adjacent to the kidney was preserved. The tumor appeared to arise in the medulla of the suprarenal, and measured 210 by 105 by 100 mm. It showed an irregular nodular surface with a capsule that was broken through in several places by the new tissue. These protruding masses were continuous with the metastases, and the enlarged lymph nodes were located retroperitoneally. The surface of the tumor was reddish purple and gray, with many hemorrhagic areas. On cross-section the tumor was found to be soft, and showed large hemorrhagic areas interspersed with yellowish patches of necrosis and grayish areas of tumor tissue. The whole was friable and soft. The appearance of the metastatic masses was much the same as that of the primary growth.

Microscopic examination revealed a rapidly growing tumor, consisting of small cells with nuclei rich in chromatin and hardly any protoplasmic rim. There were

many other cells of larger size with a large vesicular nucleus and a nucleolus which was almost as big as the nucleus of the smaller cells and deeply staining. The protoplasm took the eosin stain faintly, and showed several dendron-like protrusions. These larger cells resembled ganglion cells. Numerous fibrils could be perceived which stained yellowish brown with van Gieson's stain, but did not take Mallory's neuroglia or connective tissue stain. We could not demonstrate the purely nervous origin of these fibers as shown by Herxheimer,[17] although we had at our disposal the excellent and practical modification of Bielschowsky's silver impregnation method devised by Dr. Otani of our laboratory. Typical rosettes were not found. Numerous mitotic figures were present. Sections taken from different areas showed extensive hemorrhage, necrosis and rapid growth of

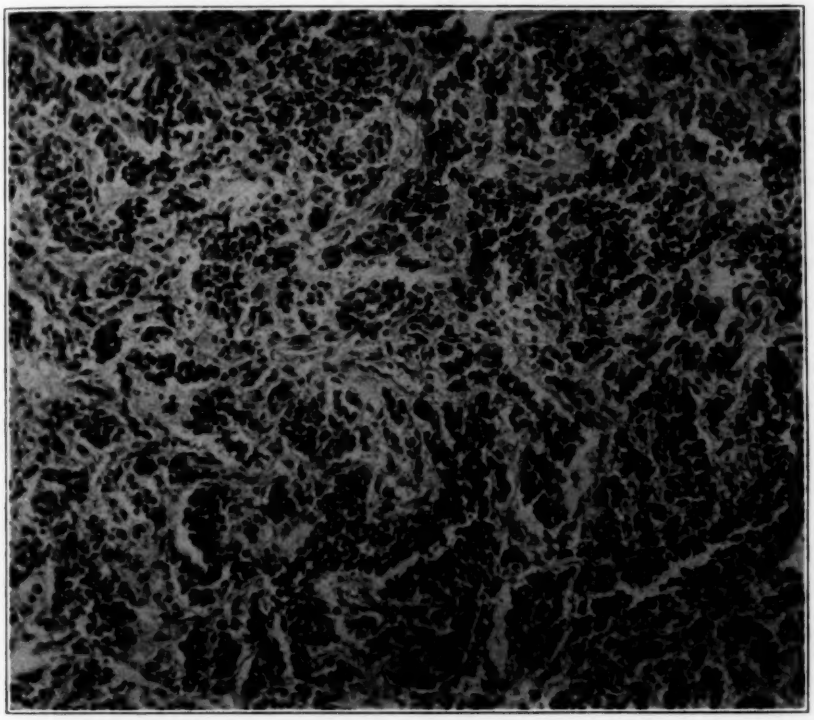

Fig. 2 (case 1).—Section from tumor showing variety of cells; fine fibrillar network between cells is seen; × 120.

the tumor. The suprarenal cortex adjacent to the upper pole of the kidney was intact; the medulla and other parts of the cortex could not be found.

Although definite proof of the nervous origin of the fibers cannot be given, and although rosettes were not found as described in previous papers, we believe that the diagnosis of neuroblastoma is indicated by the rapid clinical course, the morphology of the cells and the location of the tumor. Apparently this tumor arose from undifferentiated neuroblasts at a time when fibril formation was still in progress. Landau,[18] as a matter of fact, states that fibrils are not absolutely

17. Herxheimer, G.: Ueber Tumoren des Nebennierenmarkes, insbesondere das Neuroblastoma sympatheticum, Beitr. z. path. Anat. u. z. allg. Pathol. **57**:112, 1913.

18. Landau, M.: Die malignen Neuroblastome des Sympathicus, Frankfurt. Ztschr. f. Path. **11**:26, 1912.

necessary for a diagnosis. Numerous other authors have described typical cases, clinically and morphologically, without the presence of rosettes.

CASE 2.—C. K., a boy, aged 3 months, was referred from the clinic on Dec. 19, 1925, with a history of abdominal distention, restlessness and vomiting of one week's duration. A complete history was not obtainable, on account of difficulties with language.

At the time of admission the patient was in extreme discomfort, the abdomen being distended and tense, with marked distention of the veins of the abdomen and face, together with edema of the feet and scrotum. Dyspnea was marked, the respirations being shallow and rapid. The head was sweating; the neck did not show any enlarged glands. The heart and lungs were normal. The abdomen was tense, hard and flat to percussion. The sharp edge of the liver could be felt

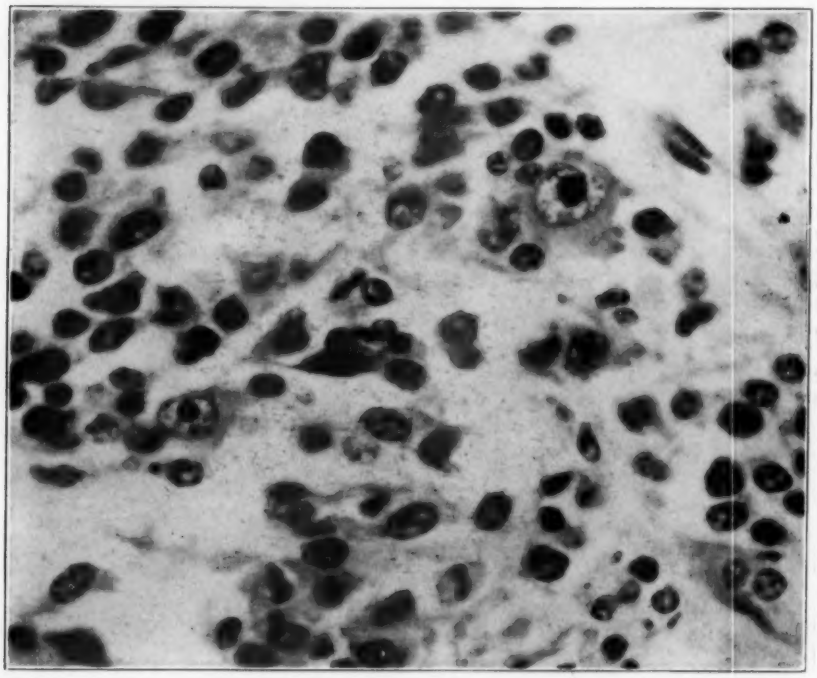

Fig. 3 (case 1).—High-power photograph showing large, ganglion-like cells, small cells with dark nuclei without protoplasm; also mitotic division figures; × 700.

4 cm. below the umbilicus, extending transversely from the level of the right iliac crest. The spleen or other masses were not palpable, and there was no evidence of fluid. Rectal examination showed the presence of a round mass about 5 cm. in diameter on the posterior wall of the abdomen.

Laboratory reports showed a red cell count of 3,344,000; hemoglobin, 48 per cent (Sahli); white cells, 11,000; polymorphonuclears, 48 per cent; small lymphocytes, 42 per cent, and large lymphocytes, 6 per cent. The icterus index was 5.7; the reaction to the van den Bergh direct test was negative; that of the indirect test was weakly positive. The Wassermann reaction was negative, as were the reactions to the Pirquet and Mantoux tests. A roentgenogram of the abdomen showed the shadow of an enlarged liver with displacement of the stomach and intestines to the left and downward, with no evidence of fluid.

The condition of the patient became rapidly worse under observation, the distention and respiratory embarrassment increasing daily despite all measures for relief. Death occurred on the evening of Dec. 25, 1925. A diagnosis of neoplasm of the liver with metastases was made. Autopsy was performed the following day, fourteen hours postmortem.

The body was that of an emaciated male infant 3 months of age. The liver was enormously enlarged, extending below the crest of the right ileum and displacing all the viscera downward. On raising the loops of intestine a large hemorrhagic tumor about 8 cm. wide could be seen spreading over the aorta, the iliac vessels and the inferior vena cava. The retroperitoneal lymph nodes were enlarged, hemorrhagic and fused.

On removal the liver proved to be large, smooth, firm and covered with numerous whitish and grayish areas of variable size. The weight was 950 Gm. On section the lobular structure was indefinite, and the tissue was firm and interspersed with numerous soft grayish-red nodules. Around the portal vein were a few enlarged lymph nodes.

Fig. 4 (case 2).—Large hemorrhagic, retroperitoneal tumor, with thickened suprarenals. The kidneys were not involved.

Both suprarenal glands appeared enlarged and thickened, and were yellow and triangular. Both were encapsulated, and rested on the upper poles of the kidney, from which they could be easily separated. On section the medulla of each appeared to be displaced by a soft, succulent, grayish-red mass which measured from 3 to 6 mm. in diameter. The cortex appeared as a mere line of compression.

The stomach contained a small submucous nodule about 3 mm. in diameter near the pyloric end. The pancreas was thickened, firm and infiltrated throughout with tumor tissue. The right testicle was brownish red; it contained a few small, indistinct grayish nodules, which looked like tumor tissue, and a small white nodule near the upper pole.

Microscopic examination showed all the tumor tissue, wherever it occurred, to be composed of numerous small cells with dark-staining nuclei and little cytoplasmic substance. There were also a few cells showing large pale nuclei with a greater amount of cytoplasm. The tumor cells invaded the liver, destroying the lobular structure. The pancreas and the testicle showed the same extensive cellular infiltration, with destruction and displacement of the parenchyma. The

medulla of the suprarenal was much thickened and composed of the same type of cells, with numerous mitotic figures throughout.

In this tumor we could not find any fibrils nor demonstrate any rosettes. However, the same considerations as in the previous tumor, as well as the clinical course and presence of extensive metastases, led us to make a diagnosis of neuroblastoma malignum. There is some question as to the origin of the tumor in this case. It may have been primary in one of the suprarenals, in the retroperitoneal tissue, or it may have originated from some of the cells of the sympathetic anlage which became detached during their descent and assumed malignant properties. We are inclined toward the latter view.

Case 3.—H. R., a boy, aged 3½, was admitted to the babies' ward on April 8, 1926, complaining of pain in the left upper quadrant, which had been constant

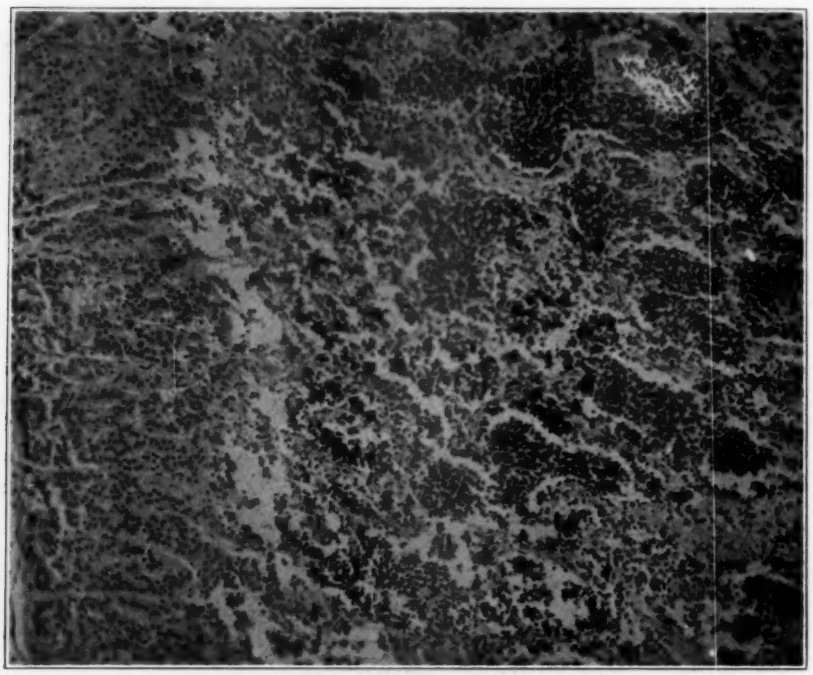

Fig. 5 (case 2).—Tumor destroying suprarenal medulla. The cortex was intact; × 120.

and had kept him from sleeping for the past three weeks. The abdomen had also been moderately distended during this time; two days before admission a physician had discovered a mass in the left upper quadrant. The pain had been accompanied by anorexia and the loss of ten pounds (4.5 Kg.) in weight during the week preceding admission. Constipation had been marked for a month. Two days before admission the child had had an epileptiform convulsion, which lasted an hour, with frothing at the mouth and involuntary defecation.

When examined the patient was weak and pale, acutely ill and showed marked recent loss of weight. There were two firm, movable masses, each about 2.5 cm. in diameter, in the left side of the neck. One of these was in the region of the left lobe of the thyroid, the other was under the belly of the sternocleidomastoid muscle. The head was normal, as was the heart. There was some dulness in the base of the left lung, but normal voice and breath sounds were heard. The abdomen was only slightly distended; there was no edema or engorgement of

the veins. There was a moderate bulging of the left upper quadrant, and a hard immovable mass was felt which extended from the costal margin to the level of the umbilicus, shading off in the midline to the epigastrium. Glands were palpable in the groin and in the left axilla. Rectal examination gave negative results.

Reactions to the Pirquet and Mantoux tests were negative; the Wassermann reaction was also negative. There were 3,592,000 red cells, with 50 per cent hemoglobin (Sahli). The white cell count was 11,600; polymorphonuclears, 75 per cent; small lymphocytes, 13 per cent; large lymphocytes, 5 per cent. Urinalysis revealed a moderate trace of protein; the sediment was loaded with pus cells. Another specimen showed many hyaline casts, a few granular casts and a moderate number of white cells. A roentgenogram of the chest did not show any abnormality, but the abdomen showed a shadow in the left upper quadrant sug-

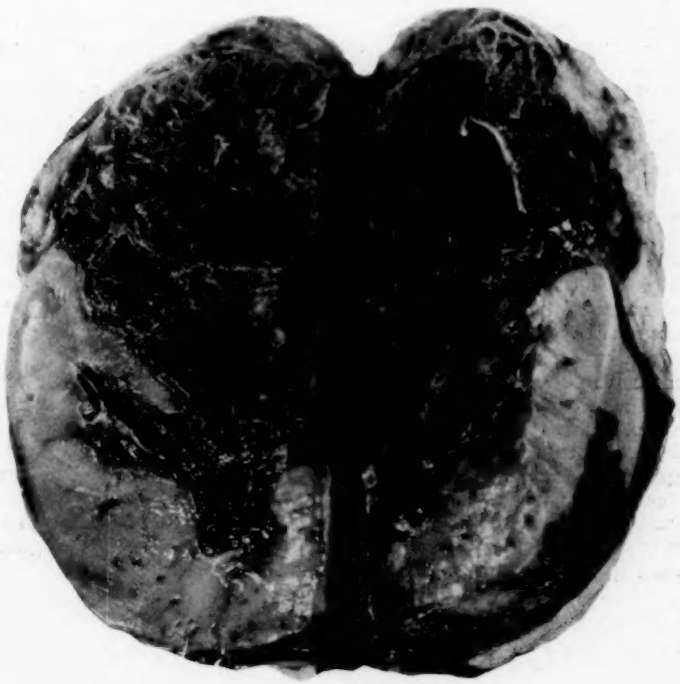

Fig. 6 (case 3).—Tumor originating in the suprarenal, compressing the kidney.

gesting tumefaction of the kidney. A roentgenogram of the long bones did not reveal anything of note.

On April 13, one of the nodes in the neck was removed for biopsy. The pathologic report described an extremely malignant metastatic tumor of doubtful origin. Operation was not advised; roentgen-ray treatments of the left upper quadrant were given several times at the urgent request of the parents.

The condition of the patient became rapidly worse, with attacks of pain and refusal to eat, complicated by occasional vomiting. The mass in the left upper quadrant became larger and more firm daily, especially after roentgen-ray treatment. The patient died suddenly on April 24, 1926, with symptoms of internal hemorrhage. A clinical diagnosis of neuroblastoma was made.

At autopsy, two hours after death, the observations were: the body was that of a moderately well developed, well nourished child, 3 years of age. The abdomen was distended, the left side being more prominent than the right. In

the left upper quadrant a large tumor mass could be felt. On the left side of the neck was a small operative incision about 4 cm. long, around which were numerous enlarged and firm lymph nodes.

The left half of the abdominal cavity was occupied by a large, rounded tumor mass which displaced all viscera to the right. The mass apparently originated from the region of the left kidney and extended to the crest of the ileum, as well as to the right of the midline. It was firm to the touch and resilient. Its anterior and left margins were circumscribed and rounded; the upper pole and the right lateral surface were uneven and nodular. The limiting capsule was broken, and many of the enlarged nodes were in continuity and contiguity with the tumor mass. These masses extended all along the original course of the retroperitoneal lymph nodes, also invading the mesentery and omentum, where they formed nodes and bloody cystic tumors varying in diameter from 1 to 6 cm. The viscera, omentum, peritoneum and mesentery had a hemorrhagic appearance. On the left side of the aorta, along the hilum of the lung and all the way up to the cervical region, there were numerous enlarged, firm, gray lymph nodes, of variable size, some partially fused. Over the pericardium was a group of six or seven confluent nodes. Both the abdominal and peritoneal sides of the diaphragm were covered with similar nodes.

On removal the tumor mass measured 35 by 25 by 20 cm. The suprarenal of the left side could not be found, apparently being replaced by the tumor. This mass was in close proximity to the kidney, and had compressed its upper pole without fusing with the substance of the kidney itself. On cross-section extensive areas of softening and hemorrhage were seen. In certain areas the tumor was grayish pink and soft; other areas were firm. The whole mass was continuous with the nodes of the abdomen, pelvis and wall of the chest. The right suprarenal was present and normal in appearance. The pancreas was diffusely enlarged, and invaded by the tumor.

Microscopic examination of the tumor and various metastases showed many small cells with dark nuclei, without recognizable cytoplasm. In some areas fine fibers could be seen between the cells. Large areas of necrosis could be seen throughout. There were confluent areas of extravasated blood with frequent erythrophages resembling the tumor cells. Mitotic figures were abundant in the tumor cells. Numerous larger cells with pale nuclei, definite nucleoli and abundant cytoplasm were present. This tumor proved to be similar to the two previously described, the differential stains reacting as before. Diagnosis was "malignant neuroblastoma arising in the left suprarenal."

SUMMARY

Within the relatively short period of eighteen months, we have observed three cases of "neuroblastoma malignum," each confirmed by autopsy. These occurred in children varying in age from 3 months to 3½ years.

Each case presented the same clinical picture of enlarged abdomen, dyspnea, extreme cachexia and anemia and a large abdominal mass with multiple metastases in various locations. The rapid and progressive courses with fatal termination in a short time were also identical. All these features correspond to the observations recorded in the literature. This characteristic behavior differs from that of other abdominal malignancies, such as the adenorhabdomyosarcoma or embryonal tumor of the kidney proper, in which the clinical course is less rapid and the metastases less frequent and widespread.

No definite rosettes could be found in any of these tumors. The nerve fibrils could be classed as nerve fibrils only by exclusion. The clinical, anatomic and topographic characteristics, however, as well as the histologic picture, did not leave any doubt in our minds as to their true nature.

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SICKLE CELL ANEMIA

REPORT OF A CASE WITH SPLENECTOMY *

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Evidence accumulated in many clinics by different observers has established beyond peradventure the existence of sickle cell anemia as a distinct clinical entity. Although the condition was first recognized by Herrick and reported as early as 1910,[1] the relatively high morbidity among negroes was not suspected prior to the reports of Huck [2] and Sydenstricker [3] in 1923. The latter found sickle cells in the blood of 0.6 per cent of a large number of negroes examined. More recently Cooley and Lee [4] examined all negroes admitted to their clinic during a period of ten months, 400 patients, and found sickle cells in 30 of them, that is, in 7.5 per cent. Such an unexpectedly high incidence should challenge one to a clearer knowledge and more ready recognition of this condition.

Sickle cells are red blood corpuscles which have assumed unusual shapes through some influence, probably a perversion of the factor which normally transforms spherical normoblasts into disk-shaped erythrocytes. The central concavity of the erythrocyte becomes displaced to one side, and its content of hemoglobin in crescent or sickle form is displaced to the other side.[5] Transitional forms of all sorts may be present, such as flattened crescents or long spindles. From the ends of many of the crescents taper off long filamentous processes, remains of the original cell membranes. Sickle cells may be present in the circulating blood, but more often the fresh blood corpuscles appear normal, assuming the sickle forms gradually, only after standing for several hours outside the body in sealed smears. The most convenient preparation is the fresh blood smear rimmed with petrolatum to prevent drying. In from twelve to twenty-four hours a large proportion of the erythro-

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2. Huck, J. G.: Sickle Cell Anaemia, Bull. Johns Hopkins Hosp. **34**:335 (Oct.) 1923.

3. Sydenstricker, V. P.; Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia. Report of Two Cases in Children, with Necropsy in One Case, Am. J. Dis. Child. **26**:132 (Aug.) 1923.

4. Cooley, T. B., and Lee, Pearl: The Sickle Cell Phenomenon, Am. J. Dis. Child. **32**:334 (Sept.) 1926.

5. Emmel, V. E.: A Study of the Erythrocytes in a Case of Severe Anemia with Elongated and Sickle-Shaped Red Blood Corpuscles, Arch. Int. Med. **20**:586 (Oct.) 1917.

cytes will have become sickle cells. This process of changing into sickle cells occurs not only in the circulating blood, but also in the bone marrow, in which even nucleated sickle cells may be found at times.

The mere presence of sickle cells does not predicate anemia. For this reason the term "sickle cell anemia" is often misleading; "sicklemia," as suggested by Cooley, especially as applied to the latent nonanemic form, would be more accurate. "Sicklemia" is a hereditary and familial condition which so far has been found only in negroes and mulattoes. It is transmitted by both men and women in accordance with the mendelian law for the inheritance of a single factor, with the sickle state dominant over the normal. The condition may be latent in a person with perfect health, and may be detected only in smears from fresh blood which have stood for several hours. Again, it may induce occasional vague symptoms with or without anemia. Finally, in its severe form it becomes the full-blown sickle cell anemia. This is a primary hemolytic anemia caused by the action of an unknown metabolic or toxic disturbance on the hematopoietic tissues, which predisposes the erythrocytes to hemolysis and phagocytosis.[6] Remissions form a striking feature of the disease, with sudden passage from the active into the latent state, and, vice versa, from the latent into the active state. The activating agents might be any factors which lower resistance. Mulherin and Houseal [7] have demonstrated sickle cells in the blood taken from the umbilical cords of two new-born infants and in the peripheral blood of two infants aged 3 days and 5 days, respectively, whose mothers had "sicklemia."

There is no relation between the severity of the clinical picture and the percentage of sickle cells present. A large proportion of the erythrocytes may become sickle cells in a person without symptoms of anemia, while the proportion may be much smaller in one with acute symptoms. There is abundant evidence of destruction of blood. The jaundice, usually mild, is seen most typically in the greenish-yellow pigmentation of the sclerae. The blood serum is bile-tinged, and the indirect van den Bergh reaction is positive. The urine contains an abnormally large amount of urobilin. Large deposits of blood pigment are present in the liver, spleen and kidneys. There are certain symptoms of sickle cell anemia which are found sometimes alone, sometimes in combination with other symptoms. There may be a mild intermittent fever up to 102 or 103 F., without apparent cause. Frequently sharp abdominal pains occur after meals, especially in the epigastrium or left hypochondrium, and may be associated with the presence of splenic

6. Sydenstricker, V. P.: Further Observations on Sickle Cell Anemia, J. A. M. A. **83**:12 (July 5) 1924.

7. Mulherin, W. A., and Houseal, R. W.: Sickle Cell Anemia from a Pediatric Point of View, Tr. Sect. Dis. Child. A. M. A., 1924, p. 77.

infarcts. There may be diffuse pains and stiffness in the muscles. An infrequent but typical observation is the circular, sharply outlined ulcer which develops over the tibia, often as the result of a slight trauma. In Emmel's case, ulcers of the leg developed at the ages of 5, 19 and 21, and all healed spontaneously. The legs should always be examined for scars resulting from old ulcers. In most cases of sickle cell anemia there is a hypochlorhydria or even an achlorhydria.

The outstanding feature of the active cases is the anemia, which is usually mild or moderate, rarely severe. The red corpuscle count ranges between 1,500,000 and 4,000,000, and the hemoglobin between 30 and 70 per cent. There is a moderate leukocytosis of 10,000 to 30,000, without much abnormality in the differential count. The red and the white cell elements show signs of active regeneration. There is a moderate amount of diffuse polychromatophilia and a slight amount of punctate basophilia. There are many normoblasts and an occasional myelocyte, and there is a greatly increased percentage of reticulated red corpuscles. The platelets are increased. Although there is considerable anisocytosis and poikilocytosis, the sickle cells often cannot be seen in the freshly stained blood smears, and hence would be overlooked in a routine examination of the blood. Phagocytosis of erythrocytes by the large mononuclears can be seen in most cases. The resistance of the red corpuscles to salt solutions is normal in sickle cell anemia, differing in this respect from other hemolytic anemias.

The mothers of "sicklemic" children usually speak of the poor health and the weakness of their children during their early years.[8] Sydenstricker states that certainly a considerable proportion of the underdevelopment seen in negro children past the age of rickets is caused by this disease. If the condition remains latent during childhood, it probably will remain latent during life. Undoubtedly its presence increases the mortality among these children in whom it is activated so easily, for they are extremely susceptible to intercurrent infections, and, according to Huck, usually die before the age of 30.

Necropsy reports on three cases are available, in all of which the abnormal conditions, as would be expected, were centered in the hematopoietic organs. In the active cases the liver was much enlarged, and the spleen was atrophic. The splenic capsule was thick, and was covered by fibrous adhesions. The splenic pulp was decreased greatly in amount, and had been replaced by much fibrous trabeculation tissue and by many small hemorrhages and infarcts.[9] In Graham's case [10] there

8. Mason, V. R.: Sickle Cell Anemia, J. A. M. A. **79**:1318 (Oct. 14) 1922.

9. Sydenstricker, V. P.: Sickle Cell Anemia, South. M. J. **17**:177 (March) 1924.

10. Graham, G. S.: A Case of Sickle Cell Anemia with Necropsy, Arch. Int. Med. **34**:778 (Dec.) 1924.

were many rounded, tumor-like areas of homogeneous, dark red, rather soft tissue which consisted of poorly developed splenic pulp engorged with blood, regenerative foci of hyperplastic tissue. There was a general lymphadenoid hyperplasia, and a hyperplasia of the bone marrow affecting both the red and the white cell elements. It was the result of some chronic injury to the marrow with repair and compensatory hyperplasia.

In addition to the cases of sickle cell anemia already mentioned, others have been reported by Washburn,[11] Moser and Shaw,[12] Jamison,[13] Marie,[14] Browne,[15] Archibald,[16] Anderson [17] and Hamilton.[18] To this group I feel justified in adding another case because of certain unusual features displayed: (1) Neither the child in question nor his parents were of direct negro descent; (2) four years previously the case had been considered pernicious anemia; (3) changes in the spleen had been observed in its transition from a hypertrophic to an atrophic organ, and (4) a new therapeutic measure in the form of splenectomy was introduced.

REPORT OF CASE

History.—F. D., aged 6 years, was seen first on June 24, 1921, at the age of 5 months, in the outpatient department of the Children's Hospital of Philadelphia, for an acute gastroenteritis. The weight at birth had been 4½ pounds (2,042 Gm.), and at this first examination was 10½ pounds (4,649 Gm.). Again at 8 months he was treated for a mild cough, at which time the weight was 16 pounds (7,262 Gm.). He was still breast-fed, and dentition was active. A few weeks later the family moved from Philadelphia to Charleston, S. C., where the mother became ill, and the child was put on a diet of condensed milk. At the age of 1 year he had an attack of pertussis. At the age of 15 months he was started on a mixed diet.

The child had returned to Philadelphia at 16 months of age, and was admitted to the Children's Hospital on June 12, 1922, because of his weak and anemic condition. The mother said that he had been sickly since the age of 10 months. On admission the weight was 15 pounds (6,802 Gm.); he was markedly anemic and had slight jaundice. The spleen was large, extending 5.5 cm. below the costal margin in the midclavicular line and presented a sharp, smooth edge and an

11. Washburn, R. E.: Peculiar Elongated and Sickle-Shaped Red Blood Corpuscles in a Case of Severe Anemia, Virginia M. Semi-Month. **15**:490 (Feb. 10) 1911.

12. Moser, R. A., and Shaw, W. J.: Sickle Cell Anemia in the Northern Negro, J. A. M. A. **84**:507 (Feb. 14) 1925.

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18. Hamilton, J. F.: A Case of Sickle Cell Anemia, U. S. Veterans' Bur. Med. Bull. **2**:497 (May) 1926.

easily palpable notch. It was movable bimanually. The liver also was enlarged, extending 4 cm. below the costal margin. There was a slight general glandular enlargement, except of the epitrochlear glands. The heart was slightly enlarged, and presented a diffuse systolic murmur. The temperature ranged between 99 and 100 F. Both parents were anemic. While under observation for one month, the child's blood picture improved somewhat, but on July 27 the patient developed measles, and was transferred to the Municipal Hospital. During August there was a persistent macular eruption on the skin, and on one occasion it was noted that the spleen was smaller. At 21 months, the weight was 18½ pounds (8,389 Gm), and there was a complaint of vague pains.

When the patient was 2½ years old (July 12, 1923), the spleen was still large and firm, extending 6 cm. below the costal margin. The liver, too, extended

Results of Examinations of the Blood

Date	Red Blood Cells	Percentage of Hemoglobin	White Blood Cells	Percentage of Polymorpho-nuclears	Percentage of Eosinophils
1/31/21	Birth				
6/13/22	1,860,000	25	32,300	59	1
6/20/22	1,800,000	28	28,300	34	3
7/ 2/22	2,640,000	39	9,800	49	2
7/ 9/22	3,130,000	37	8,600	34	2
7/12/23	2,150,000	28	18,600	29	5
8/ 3/23	3,810,000	38	8,800	29	1
3/ 9/25	3,020,000	46	30,000	68	
3/23/25	3,880,000	70	15,700	61	1
4/ 9/25	2,790,000	50	20,800	62	1
7/15/25	2,910,000	55	13,200	35	13
7/31/25	2,890,000	53			
8/12/25	3,070,000	55			
10/17/25	2,860,000	49	17,300	69	
12/ 8/25	4,100,000	68	20,200	60	
12/16/25	3,920,000	62	22,100	29	
1/26/26	3,260,000	61	24,200	56	2
4/23/26	1,650,000	50	10,800	43	4
5/ 6/26	3,508,000	60			
5/31/26	2,640,000	61	23,300	35	1
6/ 6/26	3,568,000	52	16,720	48	
6/29/26	3,130,000	61	14,400		
7/14/26	1,900,000	27	46,800	61	3
7/20/26 (transfusion)					
7/23/26	2,530,000	50			
8/17/26	3,090,000	53	10,200		
9/13/26	3,310,000	54	19,900	34	1
9/28/26 (splenectomy)					
10/ 3/26	1,490,000	49	20,800	96	
10/22/26	3,380,000	51	21,600	60	6
10/29/26	3,440,000	56	13,900	54	2
11/ 9/26	3,180,000	49	12,300	50	3
11/15/26	2,960,000	55	15,500	44	1
11/24/26	3,270,000	69	13,900	67	1
11/29/26	3,420,000	57	17,200	57	1
12/ 6/26	3,390,000	63	18,000	55	1

5 cm. below the costal margin. A diagnosis of pernicious anemia was made. Frequent examinations of the blood made at that time and subsequently are summarized in the accompanying table. The red blood corpuscles on most occasions showed marked anisocytosis, poikilocytosis and polychromatophilia, slight basic degeneration, many normoblasts and a few Howell-Jolly bodies.

The child was not seen again until March 8, 1925, at the age of 4 years, when he was admitted to the University Hospital in Philadelphia with acute pain in the upper part of the abdomen, swollen, tender ankles and fever. He had been in good health during the previous year and a half. The acute attack soon subsided. Although the blood picture remained unchanged, the spleen and liver had both decreased in size, the spleen no longer being palpable and the liver extending only 2 cm. below the costal margin. There was a slight persistent fever and leukocytosis and a mild yellowing of the sclerae. The tonsils and adenoids, which were much enlarged and were thought to offer possible foci of infection, were

removed on July 7. During the summer, several crops of macular lesions of the skin resembling those of pityriasis developed, and there was another attack of abdominal pain with fever. On Nov. 2, 1925, he developed nasal diphtheria, and one month later sinusitis, for which both maxillary antrums were opened and drained.

On April 23, 1926, another attack of abdominal pain and another crop of lesions of the skin appeared, together with a patch of pneumonia in the lower lobe of the left lung. Then for the first time sickle cells were sought and found

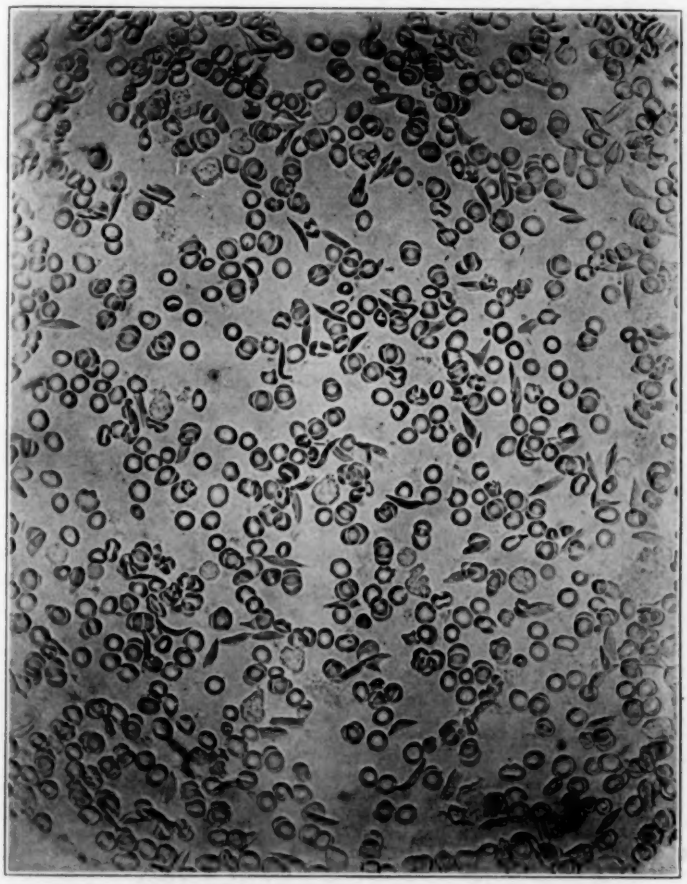

Fig. 1.—Fresh, unstained blood smear immediately after being set up.

in the blood of the patient, about 10 per cent in the fresh specimen and almost 100 per cent in a twenty-four hour specimen. The blood platelets numbered 244,000, and there were from 10 to 20 per cent of reticulated red corpuscles. The bleeding time was three minutes, and the coagulation time was four and one-half minutes. In salt solution hemolysis of the red corpuscles began at 0.42 per cent, and was complete at 0.275 per cent. The direct reaction to the van den Bergh test was negative, and the readings of the indirect reaction were from 0.75 to 2 units. An intravenous transfusion of 225 cc. of citrated blood was given on July 20, 1926, without much benefit. The patient's blood was of group II (Moss).

Later observations on the red corpuscles revealed 1 per cent of sickle forms in the fresh blood and from 50 to 70 per cent in the twenty-four hour smear.

Discovery of the sickle cells led to a closer examination of the family. The patient had the features of an octoroon: fair skin, light kinky hair, thick lips and slightly flattened nose. The father, aged 44, was a healthy white man without negro characteristics, and without sickle cells in his blood. The mother, aged 30, was also white, but had the dark skin and features of a Cuban. She had always been weak and nervous, and smears of her blood showed a small proportion of sickle cells. There were four other children, aged 11, 10, 6 and 3, all girls, the

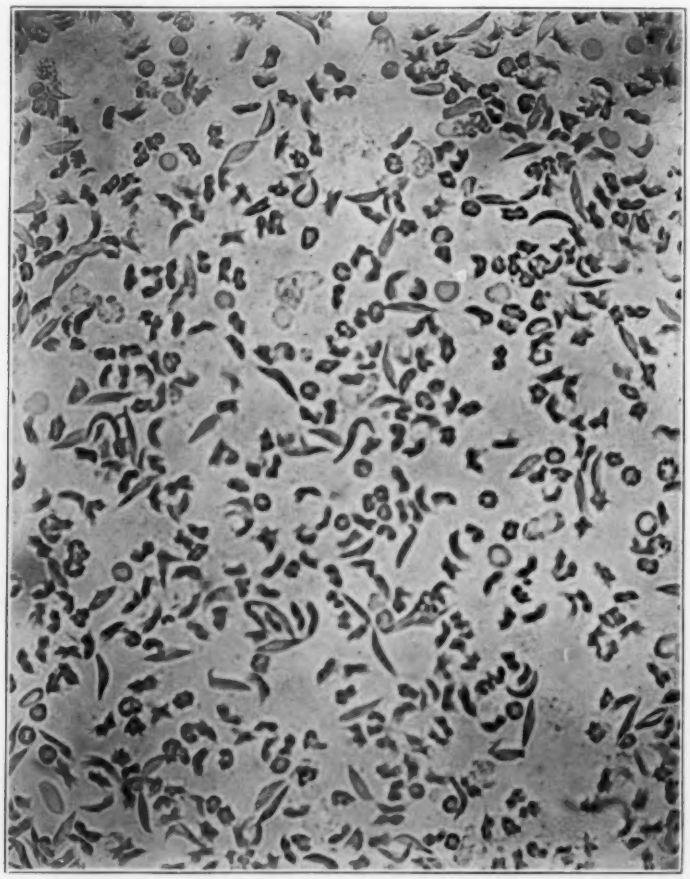

Fig. 2.—The same blood smear as in figure 1 after twelve hours.

third named being a twin of the patient. None of them had any decidedly negroid features, although the youngest had a few sickle cells in smears of her blood. The patient had not had any brothers. Neither parent knew of the existence of any negro forbears; the father's maternal grandparents were English and Jewish, and the mother's maternal grandparents were Cuban. The family lived in a district bordering on the colored section, but by their neighbors they were classed among the whites. They attended the Episcopal church.

As the patient did not show a tendency to improve during many years and continued to develop secondary infections at frequent intervals, it was decided to

attack the most prominent and easily accessible point of pathologic activity, the spleen. On Sept. 28, 1926, the spleen was removed. Its macroscopic appearance was described by Dr. Albert Bothe: "Specimen consists of a spleen which measures 8 by 4.5 by 2.5 cm. and weighs 46 Gm. The capsule is roughened in places, probably due to adhesions. On section it bulges little, is dark red and moderately firm. The malpighian bodies are just visible." The microscopic appearance was described by Dr. E. B. Krumbhaar: "The specimen is unique. There is intense congestion of both pulp and sinuses, masking most of the other features except for a peculiar fibrosis and localized calcification. The malpighian bodies are much diminished in size. There is extreme calcification of the smaller and larger vessels. There are distorted scarred areas, with much hemosiderin."

Postoperative recovery was rapid and uneventful. Two months after operation, the general condition showed little change. The process of sickle cell formation continued as before. Any further developments in this case will be reported.

Fig. 3.—The same blood smear as in figure 1 after twenty-four hours; high power magnification.

COMMENT

Several points of interest are educed by perusal of the history. If this should be an instance of sickle cell anemia in a white person, it would be the first on record. However, the facial characteristics of the patient indicate a mixture of colored with white blood at some time in the past, for which the Cuban ancestry affords distinct opportunity. The crossing of races among certain elements of the Cubans has been notorious. But in the last three generations of this family, which can be traced with certainty, there have not been any negroes. The mother and the youngest sister, whose blood has the same tendency to form sickle cells as that of the patient, but to a much less pronounced degree, are devoid of any of the usual symptoms of the disease.

It has been asked how these cases of sickle cell anemia were diagnosed in the past before the disease had been recognized. This particular case had been considered pernicious anemia. Undoubtedly, many other cases of sickle cell anemia have been placed in this same category. The frequency with which one finds "sicklemia" (latent and active) among negroes should lead to an examination of fresh smears of the blood in any disease of doubtful etiology in a negro, especially in the presence of anemia, a persistent, unexplained fever or leukocytosis or occasional attacks of abdominal pain.

This case has served to emphasize the fact that the spleen is the center of pathologic activity, as is usual in a condition in which destruction of blood predominates. However, the nature of the transition from the original hypertrophic to the subsequent atrophic state is not clear. Whether splenectomy will be of benefit in such a persistently severe type of case remains to be seen.

SUMMARY

1. All cases of sickle cell anemia which have been reported up to the present time are summarized, and current ideas on the subject are discussed.

2. Another case is reported, which occurred in an apparently white child of Cuban descent who had been observed practically from birth.

3. The spleen passed from a greatly enlarged to an atrophic condition.

4. Before the discovery of sickle cells, this case had been diagnosed pernicious anemia.

5. An attempt was made to bring about improvement by splenectomy.

DERMATOSES DUE TO LIGHT SENSITIZATION

WITH SPECIAL REFERENCE TO THE CUTANEOUS DANGERS OF ULTRAVIOLET RADIATION IN CHILDREN *

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As has been known for many years, more or less prolonged exposure to the violet and ultraviolet rays of the sun, and naturally to those artificially produced, may cause not only systemic disturbances but also inflammatory and degenerative changes in the skin, varying with the person. The harmful systemic effects have not been well understood, and I will not deal with them here, save to state that deaths of infants following short exposure to ultraviolet radiation have been reported.[1]

From a cutaneous standpoint, persons with a mild or moderate susceptibility to light, and, as has been shown, to the rays of light in the violet end of the spectrum, are not uncommon; severe reactions, however, are rare. Yet it is important to recognize that under certain circumstances, to be noted presently, a potential susceptibility or an existent cutaneous disturbance due to light sensitization may be made decidedly worse by artificial ultraviolet radiation. With positive clinical and experimental evidence to show that ultraviolet therapy is of considerable value in certain diseases, particularly in those of infants, an enormous increase in its use has occurred. Since its application in all sorts of ailments is sure to follow, it appears extremely opportune to review the subject of light sensitization and the clinical cutaneous reactions it leads to, and to report several illustrative cases with experimental notes.

PATHOGENESIS

Under normal conditions, photosensitive substances on which certain life processes depend [2] are present in living tissue. Under abnormal or pathologic conditions, an increase may occur in the amount, or perhaps in the development in vivo, of a new photosensitive substance, with resultant photodynamic effects from light previously innocuous. The rays in the solar spectrum responsible for this have been shown to be those at the short end of the visible, and at the long end of the ultra-

* Received for publication, Jan. 26, 1927.
* Read before the Philadelphia Pediatric Society, Jan. 11, 1927.
* From the Research Institute of Cutaneous Medicine, Philadelphia.

1. Pratique courante, Press méd. **77**:1214 (Sept.) 1926.

2. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 419.

violet, light.[3] Since ultraviolet radiation is universally toxic for living cells, these, when hypersensitive to visible light, are apt to develop fulminating effects under such pure radiation. The basic cause of these effects is said to be a photochemical reaction, the intricate nature of which, however, although not understood as yet, has been made the subject of considerable experimentation within recent years. Certain it is that cutaneous photochemical reactions can occur only in the presence of two factors, namely, light and a photosensitive substance. The latter must have the property of fluorescence, and such a substance produces its effects by absorbing wave lengths characteristic of it.[4] Studies to determine the photosensitive substances in the cells of the skin, or in the circulating blood selectively absorbing and rendering living cells susceptible to the toxic action of ultraviolet rays, appear to indicate that these are the porphyrins [5] and the aromatic amino-acids of the proteins.[6]

Bazin, in 1855,[7] was the first to suggest that certain skin diseases were due to the action of light; McCall Anderson [8] was the first to suggest a possible photosensitizing substance, but Ehrmann [9] appears to have been the first to suggest that hematoporphyrin acts as the sensitizing substance in hydroa vacciniforme. There is sufficient experimental evidence in both man and animals to show that this substance is photodynamic.

Further studies on the possible origin of the toxicity of ultraviolet rays were made by Harris and Hoyt in 1917. These workers came to the conclusion that the susceptibility of protoplasm to these rays was conditioned by their selective absorption by the aromatic amino-acid radicals of the proteins. They demonstrated absorption of the rays to a greater or less extent by passing them through solutions of the proteins and amino-acids. It has not as yet been demonstrated that these bear any definite relation to any cutaneous eruptions. Nevertheless, Barber and his co-workers think it probable that the sensitizing agent in the primary types of actinic eczema (sunlight eczema) is either a product of the decomposition of protein or a bacterial toxin acting on the epidermal cells and rendering them hypersensitive to light.

The clinical conditions considered as bearing a definite relation to photodynamic sensitization are so varied that it is difficult to believe that

3. Barber, H. W., et al.: Guy's Hosp. Rep., July, 1926.

4. Michael, J. C.: Critical Investigation of Relation of End-Products of Protein Metabolism to Eczema and Kindred Disorders, Arch. Dermat. & Syph. **14**:302 (Sept.) 1926.

5. Hausmann, quoted by Senear and Fink: Hydroa Vacciniforme, Arch. Dermat. & Syph. **7**:145 (Feb.) 1923.

6. Harris and Hoyt: Science **46**:318, 1917.

7. Bazin: Cours de semiotique (cutanee) 1855, quoted by Barber et al. (footnote 3).

8. Anderson, McCall: Brit. J. Dermat. **10**:1, 1898.

9. Ehrmann, S.: Arch. f. Dermat. u. Syph. **97**:75, 1909.

sunlight is the only factor concerned. However, in the present state of knowledge, the following classification is justified.

CLASSIFICATION OF CUTANEOUS LIGHT REACTIONS

The specific cutaneous sunlight reactions may be tentatively classed as of congenital and of acquired origin. A provisional classification of those which depend on congenital conditions are:

1. Pigmentations
2. Acute dermatitis solare [10]
3. Chronic dermatitis solare
4. Cheilitis actinica chronica (Ayres) [11]
5. Hydroa-vacciniforme (Bazin)
6. Summer prurigo (Hutchinson)
7. Pruritus aestevalis (Hutchinson) (?)
8. Xeroderma pigmentosum
9. Keratoses (?)

Those depending on an acquired susceptibility are:

1. Experimental
2. Acute dermatitis solare [10]
3. Primary (dermatitis of Barber and Howitt) (sunlight eczema)
4. Secondary (pellagra, lupus erythematosus, eczema, variola, roentgen-ray skin and Addison's disease)
5. Fagopyrismus or buckwheat poisoning
6. Urticaria solare (Duke)

SYMPTOMATOLOGY

Congenital Cases.—The pigmentations, both diffuse in the form of tanning and discrete in the form of freckles, are well known and are excellent illustrations of the normal individual idiosyncrasy, as well as of the natural protective mechanism to the actinic rays of the sun. Cases of melanosis have, however, been described, in which pigment reactions to even ordinary intensities of light have followed. These, as well as those in which death has followed ultraviolet radiation, may belong to the group classed by Gunther [12] under the term hematoporphyria, of which he distinguishes an acute, a chronic and a congenital form. As the acute form manifests itself by systemic disturbances and the chronic form by the cutaneous manifestations described under hydroa vacciniforme, and as infants and young children have heretofore been ordinarily protected from sunlight, it is not improbable that the congenital form has commonly escaped recognition. Acute dermatitis solare, or sunburn, as it is commonly known, does not require description; but, as with the pigmentations which it frequently precedes, it varies in degree in accordance with personal sensitiveness and the

10. Macleod, J. M. H.: Diseases of the Skin, London, H. K. Lewis Co., 1920.
11. Ayres, S.: Chronic Actinic Cheilitis, J. A. M. A. **81**:1183 (Oct. 6) 1923.
12. Gunther, Hans G.: Dermat. Wchnschr. **68**:177, 1919.

intensity of the light. Although blondes burn far more easily than do brunettes, there are persons of the latter group who burn easily. Mild reactions of acute dermatitis solare are usually considered more or less normal. On the other hand, persons liable to severe reactions soon learn this and do not frequent seashore resorts. When there is failure to diagnose susceptibility in infants of this type, marked untoward effects may follow ultraviolet radiation. Chronic dermatitis solare [10] clinically resembles a chronic radiodermatitis, but is less severe. It is seen in white people who have led a prolonged, open air existence, such as sailors and farmers, particularly in tropical and subtropical countries. The exposed surfaces of the skin are dry, atrophic and freckled, with here and there telangiectases and keratoses.

Cheilitis actinica chronica or sunburnt lip, first described by Ayres,[11] is a common condition in the south and southwest states. It is characterized by a chronic, scaly, crusted inflammation of the lip which tends to appear in the spring, continues during the summer, and disappears with the onset of cold weather.

Hydroa vacciniforme is characterized by a vesicobullous eruption (fig. 1) in which the lesions are first erythematous, vesiculation developing more or less rapidly. It affects the exposed surfaces, and appears first during the spring of the early years of life, as a rule in the third or fourth year. The attack begins about twelve to twenty-four hours after exposure to the light, and usually is preceded by itching and burning, and perhaps by mild constitutional disturbances. Small, round, semitransparent elevations of the epidermis develop on an erythematous base. These tense vesicles become enlarged, usually umbilicated, and their contents purulent. When the brownish depressed crust falls, varioliform scars remain. These scars may in time become so numerous as to cause considerable disfigurement. Exposure to the sun is followed in the usual time by another outbreak, the severity of which varies with the intensity of the light. The older the patient the greater the immunity, until, in fact, the immunity finally appears to become complete. However, the disease may begin later in life. In 1922, Senear and Fink reviewed eighty cases.[13]

Case 1.—*History.*—F. L., a white boy, aged 8 years, was referred to me because of an eruption on the exposed surfaces, which had recurred every summer for the past four years. The family and personal history revealed nothing of importance, except that a 3-year-old brother, when a baby, stained his diapers brownish red. Itching was a prominent feature of the eruption, it was particularly severe in the evenings, especially after he had been playing outdoors all day exposed to the sunlight. The condition was always better in the morning. The eruption was limited to the face, neck and forearms. The eruption was always more marked on a sunny than on a cloudy day.

13. Senear, F. E., and Fink, H. W.: Hydroa Vacciniforme Sen Cestivale, Arch. Dermat. & Syph. **7**:145 (Feb.) 1923.

Examination.—The results of the examination were negative. The skin on the face and forearms was dotted with numerous varioliform scars, the result of old lesions. Numerous crusted lesions commingled with vesicles, which varied in size.

Special Observations.—Urinalyses on two examinations were negative, as was a complete blood count, and the Wassermann reaction was negative. The chemical examination revealed bilirubin 5, and cholesterol 210; this examination of the blood otherwise did not show anything abnormal. Fragility of red cells on two occasions was normal. This was the first time a high cholesterolemia has been observed in this condition. I was not able to repeat the examination.

Fig. 1.—Hydroa vacciniforme as it appeared in a patient, aged 8. Note the numerous minute scars both on the face and on the dorsa of the hands. A few crusted lesions are still present after ten days in the hospital.

The patient's tolerance to the roentgen ray (one half of an erythema dose), infra-red and ultraviolet rays was tested against a control (fig. 2). A child's skin is about twice as sensitive to the roentgen ray as is the skin of an adult.

Recurrent summer eruption of Hutchinson, or summer prurigo, is characterized by an eruption of pale conical papules which do not leave scars, although in some instances minute central vesiculation occurs, and minute scar result. The localization, the age at which the disease is

usually seen and its seasonal recurrence are like those in hydroa vacciniforme, of which it is now generally thought to be a milder type. However, according to Walker,[14] it is commonest among girls, whereas hydroa vacciniforme is seen almost exclusively in men.

Pruritus aestevalis, or summer pruritus, described by Hutchinson, is not generally admitted to be a clinical entity. It is said to develop during the heat of the summer, but special connection with light sensitization has not been shown. It is known that pruritus may be the only symptom in experimental photodynamic sensitization.

Xeroderma pigmentosum (fig. 3), one of the rarer diseases and frequently called a family disease, usually begins during the first or second year of life in the form of a dry, rough appearance of the exposed

A B

Fig. 2.—*A* indicates a normal child; *B*, a child with hydroa vacciniforme. The same amount of ultraviolet radiation was given to each. The patient with hydroa vacciniforme showed a reaction (marked erythema over the right scapula) indicative of the higher degree of sensitiveness to actinic rays. Both patients also received definite exposures of infra-red and roentgen rays which caused no reactions, thus tending to support the statement that the harmful rays are longer than the roentgen rays and much shorter than the infra-red rays.

skin. Later, pigmented spots similar to, but usually darker than, freckles appear on these areas. The spots improve during the winter but become more marked with succeeding summers. Gradually, numerous small, white, atrophic areas develop plus telangiectases and keratoses. The latter drop off, only to reform and sooner or later to undergo malignant degeneration, which may develop as early as the fourth year.

14. Walker: Introduction to Dermatology, William Wood Co., New York, 1924.

This disease ordinarily begins in the spring or summer, and in some instances follows sunburn. The skin becomes covered with the lenticular pigmented spots to which I have referred, and soon becomes dry and covered with fine scales. Death from metastases of the malignant growths usually occurs before the twelfth year.

In 1915, Corlett,[15] in reviewing the literature and two cases of his own, came to the conclusion that in this disease there is primarily and essentially an inherited susceptibility to the chemical rays of the sun.

In the discussion, White referred to the case of an Irish child, aged 5 months, on whom freckles, and later typical xeroderma pigmentosum

Fig. 3.—Xeroderma pigmentosum as it appeared in a patient, aged 4. Note the diffuse freckling of the face and the prickle cell cancer on the lower lid. There were likewise a number of keratoses and atrophic spots; also marked photophobia.

developed after a single exposure to the February sun. If this disease is due in any part to photodynamic sensitization, either all portions of the skin are not equally sensitive or a certain immunity is developed. My patient showed no hypersensitiveness to ultraviolet radiation when he was compared with a normal control (fig. 4). Nevertheless, this condition is grouped among the cutaneous diseases due to sunlight, because of an occasional history of its development following exposure to the sun and the fact that the initial freckling becomes increasingly worse with each summer; because of the almost complete limitation to the exposed surfaces; because of its close resemblance to a chronic radiodermatitis

15. Corlett, W. T.: J. Cutan. Dis. **33**:164, 1915.

and because of the reports showing that the prognosis is better when the skin is protected from the sun. In one case at least, work as a miner has prolonged life for many years.

CASE 2.[16]—*History*—(The patient was referred to me by Dr. S. J. Gittelson.) J. H., a white boy aged 4, was born of a consanguineous marriage, the parents being first cousins. The only interesting facts in the family and personal history are that both parents have light complexions and that the father is susceptible to sun and wind; the facial skin and lips tend to become dry and chapped under prolonged exposure. A brother and sister of the patient presented no cutaneous disturbances. Marked freckling was first observed two years before presentation.

Examination.—Only the skin presented abnormalities. The skin of the face and, to a less degree, that of the dorsa of the hands presented numerous freckle-like lesions, white atrophic spots and keratotic elevations. On the left lower

A B

Fig. 4.—*A* is a patient with xeroderma pigmentosum; *B*, a normal patient. The same amount of ul.raviolet radiation was given to each, the normal patient showed the greatest reaction in the form of erythema (circled by ink just above the umbilicus) explained by the fact that the body of patients with Kaposi's disease becomes moderately pigmented in the course of time and is thus protected from acute actinic effects.

eyelid was a dime-sized ulcerative lesion which microscopically proved to be a squamous cell cancer. The skin over the covered surfaces had a curious pigmented appearance. There was marked photophobia.

Special Observation.—Urobilinogen and bilirubin studies were negative. Red cells were not abnormally fragile.

The development of keratoses in chronic dermatitis solare and in chronic radiodermatitis is common. In the latter condition, keratoses

16. Presented before the Section on Ophthalmology, College of Physicians, of Philadelphia, Nov. 18, 1926.

have been particularly observed following exposure of the affected parts to the sunlight. Some authors believe that light is a decided factor in the development of roentgen-ray carcinoma. The common localizations of keratoses on the backs of the hands and on the face likewise are suggestive, although a definite relationship has not been shown.

Acquired Cases.—Experimental photosensitization has been accomplished in animals by Hausmann [17] and in man by Meyer Betz,[18] and Martenstein [19] claims to have reproduced the lesions in cases of hydroa vacciniforme with ultraviolet radiation. It is not generally known that lesions may also occur following the internal or external use of drugs. However patients treated with certain dyes and other photodynamic substances that may become fixed in the tissues for a long time should be exposed to ultraviolet radiation with considerable caution. Patients saturated with quinine, and perhaps those exposed to ultraviolet radiation following the intravenous use of mercurochrome-220 soluble, may show a higher degree of intolerance than normal persons. A patient who, for weeks, had been receiving quinine just short of causing tinnitus aurium, developed a severe cutaneous reaction following an ordinarily harmless exposure to ultraviolet radiation. Crude coal tar, pure or in ointment, always becomes irritant to skins, even to those previously tolerant to it, when they are exposed to sunlight. In recent years it has been stated that ultraviolet radiation is an antidote for the excessive effects of roentgen-ray exposures. In my experience, such exposure of a skin which previously has been partly or completely saturated with the roentgen rays may lead to the development of a particularly rebellious form of dermatitis. Two patients, aged 12 and 14, who were being treated for acne vulgaris and who had received about one-half the total amount of roentgen rays that a normal skin will tolerate in consecutive weekly doses, twenty-four hours after being at the seashore returned with swollen lips and moderately marked redness of the cheeks. The skin rapidly became dry, scaly and thickened, and remained so for from six to eight weeks. The clinical appearance was not that of ordinary sunburn.

From time to time, reports have appeared in the literature concerning the development of a cutaneous inflammation due to sunlight, which clinically differed in no respect from ordinary eczema but altogether from the usual sunburn. According to Barber and his co-workers,[3] the clinical features are so characteristic that the condition may be diagnosed at a glance. The eruption, which appears on the uncovered parts, is at first erythematous and bright red; subsequently there is a varying amount of serous exudation as a result of the development and rupture

17. Hausmann: Biochem. Ztschr. **30**:276, 1910.
18. Meyer Betz: Deutsche Arch. f. klin. Med. **112**:476, 1913.
19. Martenstein, H.: Arch. f. Derm. u. Syph. **140**:301, 1922.

of numerous papulovesicles. The eyelids may be swollen. The acute phase is commonly followed by a chronic phase, in which the skin becomes harsh and thickened. The eruption may persist all year, being least severe during the winter, and presenting exacerbations during the summer (fig. 5). However, the clinical picture is merely that of an eczema, the causation of which is based largely on the history and on certain tests.

CASE 3.—*History*—(Sunlight eczema.)—J. M., a man, aged 39, was referred to me in July, 1926, for treatment of severe eczema of the lips, nose and cheeks.

Fig. 5.—Sunlight eczema (?) on the nose and lips. The patient is now at his best (mid-winter). The condition has been present since the age of 7, with marked exacerbations during the summer and following prolonged exposure to the sun.

The patient said that he had had his condition since the age of 7. There was nothing of special interest in the family or personal history, except that the eruption would almost disappear during the winter and recur in the spring, about March. It always became worse after exposure to the sun, and several hours later it itched so severely as to force him to rub the skin raw with a turkish towel. It is interesting to note the patient's own observation that he was always better while on an inside job, and that during a period of several years when he was manager in a moving picture theater he was almost free from the condition.

Examination.—The results of examination were negative, except for the presence of an erythematous, oozing, crusted eruption on the nose, cheeks and

lips. The skin in these areas was rough, thickened and edematous. Fissuring was a marked feature, particularly on the lips. At mid-winter, when this report was written, he was fully 95 per cent improved (fig. 5).

Special Observations.—1. Food tests revealed a positive reaction to wheat, dust, mackerel, egg, beef, tomato, rice, cabbage, coffee and chocolate.

2. Susceptibility to ultraviolet radiation was found to be considerably more marked than in normal persons exposed to the same amount of radiation (fig. 6).

3. The same amount of ultraviolet radiation as in the experiment just noted produced only a slight reaction when the part exposed had previously been

A B C

Fig. 6.—*A* indicates the effect of same amount of exposure to the ultraviolet ray in a patient with sunlight eczema; *B*, same patient with the skin painted with tyrosin solution; *C*, normal condition. The photograph does not indicate the intense reaction patient *A* presented, which became red, swollen and vesicular and persisted for almost five weeks.

painted with a 2 per cent solution of potassium hydroxide containing 1 per cent of tyrosin.

Acquired secondary actinic effects have been observed, not only in pellagra, a constitutional disturbance in which the eruption represents the earliest sign of a disease frequently fatal, but likewise in such actual dermatoses as lupus erythematosus, some eczemas, variola, Addison's

disease and roentgen-ray dermatitis. The experimental production by Mook and Weiss [20] of a typical pellagrous dermatitis in a pellagrin exposed to sunlight would appear to indicate that a photosensitizing substance circulates in the blood of these persons, which is responsible for, and which explains, the production of the eruption on the exposed surfaces. Pellagra generally begins in the spring and progresses by seasonal exacerbations, first as an erythema on the exposed parts, followed by pigmentation, desquamation and later by atrophy.

Fig. 7.—Disseminated lupus erythematosus developing within twenty-four hours after the patient had been exposed all day to the sun. The entire face and upper anterior surface of the chest were particularly involved.

It is known that diseased tissue is more susceptible to ultraviolet radiation than is normal tissue; therefore it is not difficult to understand why some patients with lupus erythematosus are highly susceptible to sunlight and ultraviolet radiation. Acute outbreaks have been observed following exposures to the ultraviolet rays. I observed a patient who

20. Mook, W. H., and Weiss, R. S.: Pellagra, Arch. Dermat. & Syph. **12**:649 (Nov.) 1925.

had two marked exacerbations, and who died during the third one, which occurred after a day spent in the fields under the hot sun (fig. 7).

According to Dixon,[21] the skin of an eczematous patient is more fluorescent than that of a normal person, which may account for its greater sensitivity. A patient who had recently suffered from an acute mercurial dermatitis, with pruritus as the only remaining symptom, developed a severe actinic dermatitis several hours after an ordinarily harmless exposure to ultraviolet radiation. Suppuration and cicatrization of smallpox lesions are said to be decreased by keeping the patient away from light. Therapeutic benefit is claimed for the infra-red light in variola. It has been noted that in Addison's disease there is sensitiveness of the skin to light. The secondary changes, due to light, that occur in skins exposed to the roentgen ray have been discussed under the heading keratoses.

It is known that the free use of buckwheat tends to cause a peculiar roughness and itching of the skin, together with other symptoms. Fagopryismus, or buckwheat poisoning,[22] is primarily a disease of animals, but it may occur in man. It is characterized in animals by a cutaneous inflammation varying from a simple erythema to a vesiculopustular and even to gangrenous dermatitis, and in man by urticaria and angioneurotic edema. Sunlight has been shown to be the exciting cause, since only animals exposed to the sun develop the dermatitis.

The term urticaria solare was first used by Duke,[23] who described the third case of a condition following exposure to sunlight and characterized by itchy hives. In the first reported case, it was found that the patient was sensitive only to the rays at the violet end of the spectrum. In Duke's case, itching, redness and edema, lasting about forty-eight hours, would follow exposure to the summer sun for several minutes, whereas a two and a half minute exposure to the winter sunlight produced itching hives and erythema. Repeated exposure appeared to increase the cutaneous tolerance so far as hives were concerned, but this procedure led to an eczematous condition of the skin.

SUMMARY

1. Cutaneous reactions to light, both normal and abnormal, are reviewed.

2. Personal susceptibility to, and the dangers of, ultraviolet radiation in patients sensitive to light is emphasized.

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21. Dixon, W. E.: Brit. M. J. **2**:499 (Sept. 19) 1925.

22. Smith, H. L.: Buckwheat Poisoning, with Report of Case in Man, Arch. Int. Med. **3**:350 (May) 1909.

23. Duke, W. W.: Asthma, Hay Fever, Urticaria, St. Louis, C. V. Mosby Company, 1925.

3. Illustrative case reports of dermatoses are given, in which light, and more particularly the rays at the violet end of the spectrum, plays a major etiologic rôle.

4. With the exception of hematoporphyrinuria, there are no diagnostic signs or symptoms of the presence of a potential light sensitization in very young children. When ultraviolet therapy is to be administered to infants, testing doses to determine tolerance or sensitivity are therefore advisable. In older children, however, a recurrent summer eruption on exposed surfaces, particularly if it is associated with scarring, should be viewed with suspicion.

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Progress in Pediatrics

CHILD HEALTH IN THE PAST*

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At the suggestion of our president, this meeting of the American Child Health Association is to consider:

How far have we come? What have we accomplished? What is our next step?

The all wise program committee has decided that a brief outline of child health work in the past would be a suitable background—a sort of dark gloomy curtain, as it were, to make our present activities stand out. I have been ordered to present the Gloom. One is apt to feel that it was only in the past, the dim past, that things were bad.

I have nothing new to offer. Twice the subject has been presented before the ancestors of this association, in the form of a presidential address; in 1913, by the late Dr. Holt, and in 1921, by Dr. Shaw. I can only hope to recall certain things which in the ever changing, ever widening field of our activities may have slipped your minds. In the intensity of our work, we are all too prone to scorn the views and proposals of those who 100 and 150 years ago were aware of the importance of child health to the nation, and who for many years spoke and wrote without effect to a selfish, unfeeling public.

BEGINNINGS OF CHILD HEALTH WORK

The beginnings of child health work occurred in Europe, almost all of them, or at any rate were suggested there before we started to carry them out. Being a nation that works hard and fast when we once get started, we soon forget the past.

And yet, if we look hard enough, we can find much wisdom—which we might have listened to with advantage. A little book with a long title, called "A Cursory Inquiry into Some of the Principal Causes of Mortality Among Children with a View to Assist in Ameliorating the State of the Rising Generation in Health, Morals, and Happiness, to which is added an Account of the Universal Dispensary for Sick Indigent Children," by John Bunnell Davis, M.D., was published in London in 1817. There are only seventy-two pages, but he urges

* Address given before the American Child Health Association, Washington, D. C., May 9, 1927.

practically everything that we are doing today: the prevention of malnutrition and disease through the advice of physicians and hospitals; popular education of parents; teaching of health habits; social service; mental hygiene; posture; proper school day; convalescent homes; home economics; subsidies for nursing mothers, and elimination of patent medicines. A fine polemic of Davis', written in 1817, follows:

"That amphibious—that mongrel race of beings who prey upon the credulous and ignorant—those Herods who murder troops of children —those bold and unblushing speculators in human life, who boast their pretended remedies—their nostrums—their secrets and their charm for all complaints, particularly for the diseases of infants, might murmur at the lessened sale of Duffy's Elixer, their carminatives, their soothing syrups, their balsams of Honey, etc., and so let them."

The earliest activities for the child in this country were aimed at his soul rather than at his body. Practically all of the little that was done was undertaken by religious societies, and it was chiefly through orphan asylums and foundling institutions. As, the world over, the majority of the inmates died in infancy and early childhood, the early preparation for the hereafter was probably wise.

CHILD LABOR

Interest in education was the next phase, and this quickly became involved with the subject of child labor. Massachusetts has the honor of the first legislation relating to child labor. In 1826, a law was passed requiring that no child under 15 should be employed in any manufacturing establishment unless he had attended some public or private school for at least three months the preceding year. In 1842, another law restricted the hours of labor for children under 12 to ten hours a day. Since 1904, when the National Child Labor Committee was formed, a constant warfare has been waged against child labor.

It is perhaps not strange that so early in our national history efforts should have been made to protect the working child, for in England during the first half of the nineteenth century the expansion of factories was so great that terrible conditions developed. It took forty-five years of constant agitation to persuade Parliament to pass a ten hour bill for child workers—and that in spite of the most startling evidence. It was shown that the Poor Law authorities of one London parish made a bargain with a far off Lancashire manufacturer to "hire" to him pauper children for his mills, but only on condition that for every twenty sound children, one idiot should be taken. One manufacturer who went into bankruptcy advertised as part of his property for sale a gang of pauper children.

FOUNDING OF SOCIETY FOR THE PREVENTION OF CRUELTY TO CHILDREN

An important event in the history of child health was the establishment in 1866 of the Society for the Prevention of Cruelty to Animals, modeled after an organization founded in England in 1823. I wonder how many remember the story of Mary Ellen. A mission worker in the slums of New York found a child who had been adopted at an early age by two drunken, disreputable individuals who were treating her with great cruelty. Being unable to get any action by appeals to the police or to any other authority, she finally went to the S. P. C. A. This was a new and startling proposition, so the matter was referred to the learned legal counsel of the society, who after mature consideration decided that, "The child being an animal," the society could act. In 1875, the Society for the Prevention of Cruelty to Children was established, of which Mary Ellen was the real, though uncredited, founder.

MORE RECENT DEVELOPMENTS

Today we are deeply interested in mental hygiene. We are perhaps rather overrun with so-called psychoanalysts and mental hygienists. It is all an important modern movement. The little that was done dealt with the child "criminal." In 1852, a Massachusetts law declared that for that hardened criminal, the truant from school, the county jail was an appropriate place of confinement, but humanely limited its term of incarceration to one year. The first Children's Court was established by Illinois in 1899—the dim past! Twenty years ago, there was not a single child guidance clinic, or anything of such a character, in the country.

Interest in the infant—as far as his life was concerned—was one of our early activities. The first scientific discussion on infant mortality was at a meeting of the National Society for the Promotion of Social Sciences in Dublin, in 1861. The causes of infant mortality were discussed. In 1871, the Social Science Association discussed it in Philadelphia, and in 1876 the first International Congress of Hygiene at Brussels emphasized the importance of instruction of parents, physicians and midwives in the care of infants.

For many years, it was realized that there was an excessive mortality among infants, especially in summer. In 1874, the New York City Board of Health issued a leaflet on infant care. In 1879, the state legislature required the city to appropriate $10,000 to pay a corps of physicians to visit the sick infants in the tenements. Just how many died per thousand born is not known. It was not until 1906, when the Bureau of the Census, having been made permanent by the law of 1902, published the first mortality report for the years 1900 to 1904, that

accurate statistics were had for any considerable part of the country. It had taken us a long time to appreciate the value of human bookkeeping.

In England, in 1538, Henry VIII ordered the incumbent of every parish to keep a true and exact copy of all christenings, weddings and deaths. Perhaps as Henry was married so many times he felt the need of such records. They were not kept for long, however. Fairly complete records exist for Geneva since 1549. But one cannot learn very much from these old records. It is somewhat confusing, to say the least, to see such items as these published in a Bill of Mortality for London for the week of September 5 to 12, 1665, the year of the plague:

Fever	832
Grief	3
Teeth	128
Rising of the Light	15
and Chrisoms	20

The last strictly medical diagnosis signifies, "Death before Christening." But since 1812, England has had complete registration of births, deaths and marriages. In 1900—as long ago as that—we had vital statistics of deaths for about 38 per cent of our population; in 1915, of births for about 31 per cent. Our infant mortality rate in 1915 for this birth registration area was 100. That same year statistics showed:

Denmark	95
Ireland	92
Switzerland	90
Holland	87
Union of South Africa	86
Sweden	76
Norway and Australia	68
New Zealand	50

In 1925, of the cities in the original birth registration area of 1915, 90.7 per cent had an infant mortality rate under 100, while in 1915 only 50.8 per cent were under 100.

It was early recognized that diarrheal disease played a tremendous part in the mortality among infants, especially among those who were bottle-fed. Milk in those days was anything that one could persuade people was milk. In 1840, Robert Hartley showed that five sixths of New York's milk supply came from cows stabled within the city. He described one barn, owned by a neighboring distillery, that housed 2,000 cows. The cows never left the barn except to go to the slaughter house when they died, or to the offal dump if they died too soon to be sold as meat. The condition of filth was unspeakable; the food was entirely distillery waste, without any hay or fresh food of any kind. The milking was done by tramps and hobos in return for the privilege of sleeping in

the barns. Stalls were rented for $5 a year, and "food" provided at 9 cents a barrel. New York had a death rate of 25; one fourth of these infants were under 1 year, and more than one-half were under 5. Even twenty-five years ago, much of New York City's milk had a bacterial count higher than ordinary sewage, and most other large cities were no better off.

The sickness and mortality among infants was so great during the summer twenty years ago that many cities had special open air hospitals. Milk was beginning to receive special attention, and in many cities milk stations or depots were established. Much money was spent in pasteurizing and modifying milk, which was handed out in a formula suited to the age. The infant was rarely seen; there was no medical supervision, no instruction of the mother and no follow-up, and when summer was over, most of the stations closed. Such was our folly then. We failed to grasp the fact, as Dr. Caroline Hedger remarked, that "Babies come separately. They can't be fed by the carload." Nor did we realize that ignorance is the most important factor in infant mortality—ignorance on the part of the mother and all too often on the part of the physician. The modern idea of the milk station is the health center, and that is not twenty years old. In 1907, the Public Health and Marine Hospital Service was able to find only 143 milk stations in twenty cities, only fifty-four of which were open the year around. All the milk from the stations in five of these cities, part of it from stations in six cities, and none at all from stations in nine cities was pasteurized. In fourteen of the twenty, milk was modified to a set formula. Today I know of forty-one cities in which 95 per cent of all milk is pasteurized. Today, we are told, there are 11,500 public health nurses; twenty years ago there were 900.

Prenatal care as a factor in reducing infant mortality was practically unthought of twenty years ago. In 1908, the pediatric department of the New York Outdoor Medical Clinic undertook prenatal supervision and instruction of all women applying to the obstetric department for care. In 1909, the Committee on Infant Social Service of the Women's Municipal League of Boston carried out an experiment to try the effect of prenatal care and supervision, and in 1911 a broader campaign was carried out in New York. It was not until 1910 that the Census Bureau published any mortality statistics for ages during the first year of life. It was known that a vast number of infants died from prematurity and congenital debility, but these figures now proved that 37 per cent of the infant mortality occurred during the first month. Slowly, very slowly, the maternity hospitals, notably in Boston and St. Louis, began to face the problem. Dr. Holt's terse remark in 1912 was all too true: "In maternity hospitals infants are tolerated as one of the unavoidable incidents of obstetric practice."

Today, as we look the situation over, we find everywhere governmental activity, national and local. Government is, and ought to be, so closely connected with the child health movement that it almost seems as if they had always been so united. And yet the first city division of child hygiene is not quite 19 years old—New York established it in 1908. Today every state in the Union except Vermont has a division of child hygiene or its equivalent. In 1913—fourteen years ago—New York State established the first. The Public Health Service was the only national governmental agency interesting itself, even sporadically, in child health, until in 1912 the Children's Bureau was established. In 1927, the National Treasury will provide $1,141,000 for child health activities. Twenty years ago it spent nothing. How is all this money from national, state, and city funds being spent? We shall hear and see something about it during this meeting.

It would seem as if that tremendous organization, the public school system, would have been a natural agency through which the attack on older children might have been made. Unfortunately, it has been the most unresponsive. Medical inspection in the schools was begun in 1892, if we may say it did then, for in that year New York City appointed one medical school officer. In 1894, Boston provided fifty physicians, one for each school district, to detect communicable diseases. Chicago, not to be outdone, the following year divided the city into nine districts and appointed an inspector for each district for a similar purpose. As each district covered approximately 20 square miles, it is easy to imagine how complete the work must have been. In 1897, five years after the appointment of its lone medical school officer, New York appointed 134 medical inspectors to visit each school daily, to exclude infectious diseases.

Connecticut made the first move to go further than exclusion of infection by requiring that every child in the public schools should have his eyes examined during the fall term, and parents and guardians were to be informed in writing of the exact abnormal conditions—another example of good intentions flavored with New England thrift, for all this was to be done by the superintendent, principal, or teacher in the school.

The first utilization of trained nurses in the schools was in New York, in 1902. In 1905, just twenty-two years ago, the same city inaugurated a system of examination of every child for uncorrected defects. In 1908, there had been established some system of so-called medical inspection in the cities of Massachusetts and in seventy other places. We have had twenty years in which to develop our medical school program. How far have we perfected it?

But all this was, in a sense, negative. We were trying to find things that were wrong already. We were not trying to build up a sound

system of education of the individual in the habits of health. We were mopping up the floor, instead of repairing the leak. To be sure, in 1850, Massachusetts made the teaching of physiology compulsory in the elementary schools. Imagine how fascinating it must have been, as taught in the elementary schools of that day. It was in 1904 that in Livingston County, Illinois, 3,000 children were organized as Open Air Crusaders, to develop habits of cleanliness, proper hours of sleep, prevention of infection, etc. But it was really not until the war that such procedures were generally adopted.

We are now well provided—perhaps overprovided—with health literature of the most attractive kind, constructed to suit the minds of human beings from infancy to old age. Have any of you ever read Dr. Chavasse's "Advice to a Mother"? Sixty years ago it was the "best seller" of its kind—because the only one. It was written in the popular question by the mother—answer by the doctor style, and began thus:

"Q. I wish to consult you on many subjects appertaining to the management and care of children. Will you favor me with your advice and counsel?

"A. I shall be happy to accede to your request, and give you the fruits of my experience in the clearest manner I am able, and in the simplest language I can command, freed from all technicalities," and so on for a full page.

Poor mothers!

We have been teaching mothers, and even fathers, to demand advice as to how to keep their children well—creating the demand. How far have we gone in providing the supply? When I graduated from the medical school, I was told nothing except the barest fundamentals of the care of infants, and I learned little of that. I have begun to get a little sensitive in saying just when that was, since a group of medical students took their hats off to me on the street—but it was in this century, anyway. And with practically no exception, I believe, the same condition existed in all the medical schools. The normal was mentioned only to bring out the abnormal. The physicians were only concerned with, or only the least bit interested in, their patients when they were sick. How far have we gone along these lines? How strongly are we impressing on the physicians-in-the-making that their chief credit comes from keeping their patients well? That does not apply to the surgeon, whose main object in life is to deprive us of something!

It is a difficult thing in a short paper to bring out all I should like to present. I have not done it well, but I have tried to bring up some conditions in the past and to emphasize, by contrast, the tremendous increase in our activity, and the more rational methods that we think we have developed. The most striking thing to me in it all is how

utterly stupid we were in not seeing how inadequate our methods were. Everyone seemed to be looking for one way to solve the problem. We failed to grasp the obvious fact that the road to child health was long and had many turnings, and that coordination and cooperation were essential to success. We thought once that issuing modified pasteurized milk during the summer would make a big impression on the mortality of infants. That belonged to the last generation of young enthusiastic workers, and those of today laugh at it. We old fogies blush. Today we are beginning to realize the advantage of stock taking—of balancing our books. We welcome disinterested evaluation of our work. Twenty years ago, we felt that we must be right because we thought so. The City of Washington is to be congratulated that there is to be a social survey of its many health and welfare activities. The capital of our country wants to know whether it is doing the best that can be done. In the discussions that come later in our meeting let us always keep in mind, "Is this really effective—are we really using every opportunity to do a complete job—will the next generation laugh, with reason, at us for being stupid?" Perhaps we will find out that we can do the job more effectively. What is our next step?

News and Comment

APPOINTMENT OF DR. DE LANGE

Dr. Cornelia de Lange has been made Professor of Pediatrics at the University of Amsterdam. She is the first woman to be appointed to a professorship in pediatrics or to any other professorship in Holland.

NEW FOREIGN MEMBERS OF AMERICAN PEDIATRIC SOCIETY

At the recent meeting of the American Pediatric Society on Chesapeake Bay, Prof. Luis Morquio of Montevideo, Uruguay, was elected to honorary membership and Prof. Leon Velasco Blanco of Buenos Aires and Prof. A. Aballi of Havana were elected to associate memberships.

THE ABRAHAM JACOBI MEMORIAL FUND

The Abraham Jacobi Memorial Fund Committee of the Section of Diseases of Children in the American Medical Association reports that it has on hand a sinking fund of $2,000, and that there will be a determined effort to increase this materially during the year 1927-1928. This fund is used for the purpose of paying the expenses of foreign guests to the meeting of the Section and to encourage pediatric research; it is also frequently used to meet emergency expenses of the Section. The secretary of the Fund Committee is Dr. Frank C. Neff, 214 Medical Arts Building, Kansas City, Mo.

"CHILD DEVELOPMENT ABSTRACTS"

Volume one, number one, of publications by the National Research Council, subject "Child Development Abstracts," has been received. This consists of abstracts from *The Wistar Institute Bibliographic Service, American Journal of Diseases of Children, Journal of Nervous and Mental Diseases, Archives of Neurology and Psychiatry, Psychological Abstracts, Physiological Abstracts, Biological Abstracts, Chemical Abstracts and Endocrinology* by a committee appointed by the National Research Council. It contains 268 abstracts (twenty-three typewritten pages) and will be of great service to any one especially interested in the subject. If a copy is desired, an appeal should be addressed to Dr. L. R. Marston, Committee on Child Development, National Research Council, Washington, D. C.

CHILD MORTALITY IN HOLLAND

In the report of a state committee appointed to investigate the maternity aid in Holland, some interesting figures about child mortality in that country are given. Between 1917 and 1920, the total mortality of children under 1 year was 94.1 in 1,000; between 1921 and 1925, it decreased to 69.7, a reduction of 25.9 per cent.

Between 1917 and 1920, the mortality in the first week of life was 20.3; between 1921 and 1925, it decreased to 17.5—a reduction of 13.8 per cent. The

same figures for the mortality in the first month of life demonstrated a reduction of 19.4 per cent and for the mortality between 1 and 3 months, 30.5 per cent.

From these and other figures it may be concluded that the important reduction of the infant mortality in Holland is due principally to the decrease in the mortality of infants above the age of 1 month, and that the reduction is only in small part due to a change in the death rate of children under 1 month. Of 100 children who died in the first year of life during the years 1923, 1924 and 1925, respectively, 28.7, 31.1 and 29.3, died in the first month.

Obituary

ABRAHAM ZINGHER, M.D.

1885-1927

Abraham Zingher of New York was asphyxiated in his laboratory at the Willard Parker Hospital on June 5. Dr. Zingher's work as director of the bureau of laboratories of the New York City Department of Health has been outstanding with regard to immunization against diphtheria and scarlet fever. It is regrettable that a man of Dr. Zingher's age (42 years) should have been taken at a time when he was at the height of his usefulness. He was noted for his industry and for his keen interpretation of results. At the time of his death, he was assistant professor of bacteriology at the University and Bellevue Hospital Medical College and clinical professor of pediatrics at the New York Polyclinic. He was, of course, on the staff of the Willard Parker Hospital.

Abstracts from Current Literature

Anatomy and Physiology

THE THYMUS GLAND. W. WALTER WASSON, Arch. Otolaryng. **4**:495 (Dec.) 1926.

This is a study of 135 children under 2 years of age, thirteen of whom were studied from birth to the age of 3. Serial roentgenograms with elaborate and careful technic were made immediately before and just after death in order to study the shadow of the thymus. By this method, the thymus gland in infants under 2 years of age can be accurately portrayed in a high percentage of cases. The great vessels form a triangular shadow which greatly narrows as it passes upward toward the first rib. At its narrowest point it is less than the transverse diameter of the shadow of the spinal column. "If the thymus is present in any considerable size, it will be found to overlap the base of the heart and to pass upward, obscuring the shadow, just described, of the great vessels. The shadow of this thymus is again triangular in shape with its base overlapping the base of the heart and especially the auricles." The transverse diameter of the thymus shadow, which is usually the third interspace, may be two or three times the diameter of the shadow cast by the thoracic spine. If the shadow of the thymus is no greater than that cast by the great vessels, it is a small thymus. Owing to the consistency and location of the thymus, it can only spread laterally and downward. "The anteroposterior diameter of the thymus is that of the distance between the tracheal shadow and that of the manubrium and sternum." This shadow blends with the mediastinum. The superior vena cava or a prominent pulmonary artery may be mistaken for the left lobe of the thymus. "Enlarged mediastinal glands should be recognized either by the character of their shadows, or by the associated pathologic change at the hilum of either lung." The exposure is one-twentieth of a second in the recumbent position at full inspiration. The thymus cannot grow anteriorly or posteriorly except under unusual conditions. The size of the gland varies, not only in different infants, but also at different times in the same infant. In many infants the thymus was small at birth, grew until the age of from 10 to 14 months and gradually receded until 28 to 32 months, when the mediastinum was no longer broadened and the gland became small.

The author's classification based on size is: (1) those which do not increase the transverse diameter of the mediastinal shadow; (2) those which are twice the diameter of the body of the thoracic vertebra at the second or third interspace; (3) those which are three or more times the width of the thoracic vertebra, or the large thymus. Underweight children are likely to have a small thymus and overweight children a large thymus. Therefore, roentgen-ray examination is especially indicated in overweight children. As the thymus varies from time to time, the examination should be made immediately before operation. The author personally fears operation on children over 2 years of age who have large thymus glands. He recommends roentgen-ray treatment if the children are over 2 years of age. If they are under 2 years, this should be done only when an operation is contemplated, or when the infant has symptoms referable to the thymus.

HUNTER, Philadelphia.

Pathology, Bacteriology and Biochemistry

CARBOHYDRATE METABOLISM: II. EFFECT OF ALKALINE PHOSPHATES AND OTHER ELECTROLYTES IN CARBOHYDRATE METABOLISM. B. KOBORI, Biochem. Ztschr. **180**:218 (Jan. 11) 1927.

The addition of organic phosphate to glucose, cane sugar or rice flour feedings in animals decreased the glycogen formation, the carbon dioxide production and the respiratory quotient. Other electrolytes, as calcium chloride and sodium bicarbonate, had similar effects. In some cases, the carbohydrate metabolism was inhibited to such a degree that the condition was the same as when the animal was fasting.

THE SUBSTITUTION OF SUGAR BY OTHER CHEMICAL SUBSTANCES TO COUNTERACT AND PREVENT THE SYMPTOMS ASSOCIATED WITH INSULIN HYPOGLYCEMIA. F. SILBERSTIEN, J. FREUD and T. REVESZ, Biochem. Ztschr. **181**:327 (Feb. 17) 1927.

The experiments were performed first on dogs and guinea-pigs, and later only on guinea-pigs, because dogs did not always have convulsions associated with the hypoglycemia following the injection of insulin. Dioxyacetone (from 3 to 5 Gm.) given subcutaneously at the same time as insulin (one unit per 100 to 300 Gm. of weight) prevented the convulsions, but the hypoglycemia, although less in degree, was prolonged. Dioxyacetone given after the convulsions appeared stopped them promptly, but the blood sugar did not rise more rapidly than in the controls. This substance acted as promptly as glucose in checking the convulsions associated with hypoglycemia. No effect was obtained with alcohol or glycerin, and the result with lactates was inconstant. The authors agree with other investigators, that the property of insulin to reduce blood sugar is independent of the property which causes convulsions.

SERUM CALCIUM IN BERIBERI. A. UNGAR, Biochem. Ztschr. **180**:357 (Jan. 29) 1927.

The convulsions in experimental beriberi in doves is not due to a diminution in the serum calcium.

BRAHDY, New York.

THE INFLUENCING OF THE INORGANIC PHOSPHATE OF SERUM BY THE ORAL ADMINISTRATION OF PHOSPHATE. W. RÖCKEMANN and R. STOFFEL, Ztschr. f. Kinderh. **41**:661, 1927.

By the oral administration of disodium acid phosphate and monosodium acid phosphate, etc., it is possible to raise the content of inorganic phosphate in the serum of children. Food such as whole milk, rich in phosphorous, under definite conditions, may influence the inorganic phosphate of the blood serum.

ALBUMIN AND UREA FEVER. WALTER BAUMECKER and LUDWIG SCHÖNTHAL, Ztschr. f. Kinderh. **41**:669, 1927.

In albumin fever, there is an increase of urea in the blood and an increased diuresis. On the basis of this fact, researches were undertaken in which infants were given, besides concentrated food in general, an added amount of albumin in doses corresponding to the nitrogen need. In the majority of cases an increase of temperature occurred, which acted like a relative water starvation

fever. In comparison between albumin fever and urea fever, it was established that the latter set in later and the temperature rose less sharply.

Moreover, in urea research, there occurred a quicker excretion of the surplus nitrogen quantity and a stronger diuresis than in the experiment with albumin.

The authors' view is that the giving of a considerable quantity of albumin leads, not directly to a dynamic albumin fever, but directly to a relative water starvation fever by increase of the water output.

EMERSON, Boston.

HEPATOLENTICULAR DEGENERATION. A CLINICAL, ANATOMIC AND EXPERIMENTAL STUDY. IVAN MAHAIM, Schweiz. Arch. f. Neurol. u. Psychiat. **16**:283, 1926.

In summarizing the subject of hepatolenticular degeneration, Mahaim stated that his purpose was to produce primary, chronic lesions of the liver and to see whether these would result in lesions of the brain. Two of five dogs operated on lived sufficiently long to fill the requirements. The first dog had received four injections of 50 per cent alcohol in 40 cc. doses through the biliary passages. He lived thirty-one days after the first intrahepatic injection without presenting any neurologic symptoms. Icterus was marked. The second dog had received two intrahepatic injections of 50 per cent ethyl alcohol. He lived seventy-nine days after the first injection without presenting any clinical symptoms. There was intense icterus and a progressive cachexia.

The livers of these animals showed marked changes of the hepatic cells with biliary pigmentation and some inflammatory reaction. The brain showed alterations of the nerve cells, with some predominance in the cortex, and vascular and glial changes of the central nuclei, chiefly of the thalamus and the caudate nucleus. These reactions were not present to any degree in the cortex. while one at first got the impression that the brain structure was uniformly involved, a closer study revealed the singular fact that the vessels of the nuclei alone were markedly damaged. The lesions of the nerve cells were regarded as a general reaction and those of the vessels and the neuroglia as more specific reactions of the central nuclei. The objection might be raised that the cerebral disturbances resulted from the absorption of alcohol rather than through the intermediate hepatic changes. Control injections eliminated this possibility. It is noteworthy that neither of the two animals developed symptoms that bore any clinical resemblance to hepatolenticular degeneration.

While the general conclusions of Kirschbaum, who also worked along these lines, did not agree with those of Mahaim, it is a striking fact that the only dog in which Kirschbaum produced primary chronic changes in the liver was the only animal that also presented distinct alterations of the central nuclei.

Mahaim concluded his series of articles with an enumeration of the following points: (1) It is legitimate, as Hall proposed, to include the three diseases, Wilson's disease, pseudosclerosis and torsion spasm, in a common group known as hepatolenticular degeneration. (2) Athetotic movements appear as a result of destructive lesions of the pallidum, although lesions elsewhere may also be present. (3) The existence of pseudosclerosis without hepatic cirrhosis has not been demonstrated. (4) Primary lesions of the liver parenchyma may be produced by the injection of dilute alcohol into the biliary passages. (5) Primary chronic lesions of the liver of a dog produced grave generalized alterations of the nerve cells of the brain, which are a little less pronounced in the central nuclei than in the cortex. (6) Primary chronic lesions of the liver of a dog will provoke vascular and neuroglial alterations that involve the central nuclei,

principally the caudate nucleus and the thalamus. Similar changes in the cortex are insignificant. They manifest themselves as early as one month after the onset of the changes in the liver. (7) These experiments make it seem probable that hepatic changes are initial in hepatolenticular degeneration. These experiments do not give any information as to the cause of the hepatic involvement.

WOLTMAN, Rochester, Minn.

NEW TYPE OF PHARMACOLOGIC EFFECT ON THE RETICULO-ENDOTHELIAL SYSTEM. M. JANCSO, Orvosi hetil. **71**:209, 1927.

The author has studied with great ingenuity the effect of crystalloid substances, mostly protoplasma poisons, on the reticulo-endothelial system. Up to the present, it was known that only electronegative colloidal substances will accumulate in the reticulo-endothelial system. The work of the author has proved the fact, which previously seemed improbable, that even crystalloid basic substances may accumulate in the reticulo-endothelial system if they are injected absorbed by colloids that are known to have affinity for that system. In his experiments he used fine India ink, and crystalloid substances like arsenic acid were made to absorb in the disperse phase of the colloids. The substances rendered reticulo-endotheliotrope by this method accumulate in the reticulo-endothelial system and have a selective effect on the cells of this system. The investigations of the author widened the knowledge of the absorbing functions of the reticulo-endothelial system. They make it possible to plan a selective effect on the reticulo-endothelial system by different substances and also on the hematopoietic organs and on certain pathologic growths of the type of histocytes. The results of the investigations seem to prove that the mechanism of the effect of certain poisons can be changed without touching the chemical structure. They also give some new ideas about the so-called blockade experiments first shown by Lepehne and Eppinger.

ZENTAY, St. Louis.

Nutrition

BREAST FEEDING PROBLEMS WITH THE NEWLY BORN. C. ULYSSES MOORE and H. G. DENNIS, Internat. Clin. **4**:112, 1926.

The infants most urgently in need of breast milk, the weak, the immature and the sick, are most frequently deprived of it because they are too weak to stimulate the breasts properly. The measures suggested to overcome this difficulty are: Putting the baby to both breasts at each nursing; manual stripping of each breast for ten minutes five times a day; increasing the baby's strength by complementary feedings of expressed milk together with sufficient formula to supply the needed amount of food. The formula should taste no sweeter than breast milk.

SMITH, Ogden, Utah.

THE VALUE OF BUTTER IN THE DIET. C. ULYSSES MOORE, Northwest Med. **26**:29 (Jan.) 1927.

Moore divided a litter of eight English bull pups into two groups fed on diets equivalent in fat, carbohydrate, protein and salts, except that one group received its fat as butter and the other group as vegetable fat. The experiment was carried on almost two months. The group fed butter increased in weight from an average of 15.64 to 46.37 pounds, and the group fed vegetable

fat from an average of 15.77 to an average of 32.97 pounds. Of the latter group, one died of pneumonia and the others were weak and sickly. Roentgenograms showed their bones to be less well calcified and the teeth poorly enameled. Moore says clinical experience indicates that children react in a similar manner.

OBESITY AND THINNESS. STUDIES ON THE SPECIFIC DYNAMIC ACTION IN THEM OF PROTEIN. EDWARD H. MASON, Northwest Med. **26**:143 (March) 1927.

Certain amino-acids in the process of their oxidation cause a specific stimulation, which raises the body cells to a higher level of heat production. Observers have found that in obese persons this specific dynamic action is diminished. Mason's investigation consisted of feeding obese and normal patients a meal of 200 Gm. of lean beef after determining their basal metabolism and then determining the total metabolism hourly for four hours. He found that in simple obesity the specific dynamic action of protein is much decreased. This is also the case in hypophysial obesity. In one case of constitutional thinness, there is an increased specific dynamic action for protein.

SCOTT, Philadelphia.

THE ACTION OF INSULIN ON THE MOTILITY AND THE EVACUATION OF THE STOMACH IN NORMAL AND PATHOLOGIC CONDITIONS. D. SIMICI, G. GIUREA, C. DIMITRIU, Arch. d. mal. de l'app. digestif. **17**:17, 1927.

The motility of the stomach was studied graphically in man after intravenous injection of 15 units of insulin. For this purpose, pear-shaped rubber balls were introduced into the stomach and inflated, and the compression through the action of the stomach wall was registered with the usual methods. In another series the evacuation of the stomach was studied by the roentgen ray. The results of this work show that the insulin has an energetic action on the motility and evacuation of the stomach. It produces an exaggeration of the contractile movements and at the same time stimulates the evacuation. For this reason, the authors think that it could be used in the treatment of certain forms of gastric atonia whether or not it is accompanied by depressive troubles of secretion and by general malnutrition.

ZENTAY, St. Louis.

DIASTASE CONTENT OF COW'S MILK UNDER PATHOLOGIC CONDITIONS. T. CHRZASZCZ and C. GORALOWNA, Biochem. Ztschr. **180**:263 (Jan. 29) 1927.

The authors examined the milk of cows with hoof and mouth disease and found an increase in the diastase before clinical signs of the disease were manifest. The diastatic content remained high throughout the disease and decreased during convalescence. There was a similar variation in a few other diseases. Other enzymes did not show any constant variations.

EFFECT OF FEEDING ON THE ENZYME CONTENT OF MILK. T. CHRZASZCZ and C. GORALOWNA, Biochem. Ztschr. **180**:347 (Jan. 29) 1927.

Diastase, aldehydrase, and catalase are present in the last part of the milkings from normal cows. Peroxidase predominates in the early part of the milking. The nature of the fodder has little effect on the enzymes, except that green fodder increases the catalase.

INDIVIDUAL VARIATIONS OF THE ISOELECTRIC POINT OF HUMAN MILK. F. TRENDTL, Biochem. Ztschr. **180**:371 (Jan. 29) 1927.

Trendtl confirms Hugo Meyer's observation that the heat precipitation point of the casein, and Ylppö's observation that the isoelectric point of human milk are constant for the same woman but vary in different women.

BRAHDY, New York.

THE ACTION OF SINGLE ELEMENT NUTRITION ON THE CONDITIONAL REFLEXES OF CHILDREN. A. IUSCHTSCHENKO, Jahrb. f. Kinderh. **115**:261, 1927.

Three children (aged 7, 7, and 13 years, respectively) were studied. One was fed carbohydrate (rice gruel), one protein (Holland cheese), and one fat (butter). The three children were of different nervous constitutions. Feeding a single food element influences the conditional reactions within twenty-four hours. After two days, the decline in the reflexes is obvious. The original work must be consulted for details.

BLOOD SUGAR REGULATION IN RACHITIS. J. KÖNIG and G. LENART, Jahrb. f. Kinderh. **115**:271, 1927.

Starvation blood sugars were taken in the morning after eight hour fasts. Infants were then given 1.25 Gm. of dextrose per kilogram (in 10 per cent tea solution) by mouth. Blood was then taken at 30, 50, 70, 90, and 120 minute intervals. The sugar was determined by a modified Bang micromethod. The accompanying tables show the results.

Well Infants

		Blood Sugar After Dextrose						
No.	Age	0	30	50	70	90	120	Quotient
1	6	0.082	0.119	0.092	0.078	0.069	0.061	1.45
2	6	0.070	0.086	0.068	0.068	0.080	0.070	1.20
3	12	0.108	0.148	0.095	.....	0.112	0.080	1.42
4	13	0.077	0.083	0.102	0.079	0.079	0.076	1.31

Rachitic Infants

		Blood Sugar After Dextrose						
No.	Age	0	30	50	70	90	120	Quotient
1	15	0.069	0.097	0.141	0.082	0.086	0.078	2.04
2	6	0.097	0.118	0.123	0.150	0.100	0.097	1.55
3	16	0.062	0.083	0.104	0.187	0.096	0.075	3.01
4	7	0.086	0.176	0.181	0.102	0.092	0.083	2.10
5	6	0.089	0.120	0.134	0.106	0.102	0.086	1.51
6	8	0.087	0.176	0.124	0.087	0.098	0.095	2.02
7	5	0.082	0.104	0.119	0.108	0.094	0.083	1.45
8	8	0.105	0.130	0.147	0.105	0.076	.....	1.40

Averages

	Fasting	Maximum	Quotient	Maximum in Minutes	Return in Minutes
Well infants	0.083	0.114	1.37	35	50
Rachitic infants	0.082	0.162	1.98	53	90

These tables indicate a disturbance in the exogenous sugar regulation. The cause is either in the elevated tonus of the sympathetic nervous system or in the changed ability of the tissues to utilize sugar.

THE PATHOLOGY OF INTOXICATION IN INFANTS. ROLE OF PROTEIN. E. KRAMAR, Jahrb. f. Kinderh. **115**:289, 1927.

Dogs used in these experiments were fed concentrated milk and cane sugar, and cream, cane sugar, lactose, wheat starch, and salt mixture. From 120 to 150 calories per kilogram was fed; no water was given. On the fifth day of feeding, all three dogs on concentrated milk showed symptoms of intoxication. The three dogs fed low protein showed no toxic symptoms. The first group showed a severe anhydremia; the second group showed none. Three dogs were then fed the low protein diet further concentrated and showed no intoxication. Another group of three dogs were fed the low protein diet further concentrated. One dog died of pneumonia; the other two showed intoxication on the seventh day. Three dogs, aged 10 days, were fed 40 Gm. of vegetable oil, 20 Gm. of wheat starch, 10 Gm. of cane sugar, 10 Gm. of lactose, and 1.5 Gm. of salt mixture. They lost weight from the beginning and died of exhaustion on the fourth day without intoxication. PETERMAN, Milwaukee.

RICKETS AND THE MORPHOLOGIC BLOOD PICTURE. EUGEN STRANSKY and ALEXANDER WITTENBERG, Ztschr. f. Kinderh. **41**:585, 1927.

To the authors it seems that there is a connection between rickets and anemia in infants. The anemia rests on a hypofunction of the marrow and is recognized by the diminished number of young forms of the red and white elements and by the low number of platelets. While the blood picture cannot be accepted as a specific one for rickets, the connection is obvious. Since improvement in the blood components runs parallel with improvement of the rickets and the improvement in the blood sets in rapidly under specific antirachitic treatment, the authors believe that the examination of the blood is a clinical help to enable one to judge of the severity and of the actual stage of rickets.

THE FEEDING OF PREMATURE INFANTS IN THE FIRST WEEKS OF LIFE. H. LANGER, Ztschr. f. Kinderh. **41**:598, 1927.

On the ground of comparative observations in 115 premature infants weighing up to 2,000 Gm., the most appropriate manner of feeding, judged by the condition of nutrition, was found to be the giving of a minimum amount of food; that is, a diet that contained, on the average for the month, 75 calories per kilogram of body weight. With the minimum feeding, the gain in weight in the first month was greater; the weight was doubled more quickly, and the number of intestinal disturbances was smaller than with the so-called normal nutrition with an average of 110 calories per kilogram of body weight. It is essential for the successful carrying out of minimum feeding to add albumin to human milk, such as larosan or plasmon, 2 per cent. Once the premature infant is past the first month, the increase in the quantity of food can and must be made up to an average of 110 calories.

WATER AND INFANTS WITH FEVER. LOTTE HIRSCH, Ztschr. f. Kinderh. **41**:653, 1927.

In infants having fever, there is a definite water reduction, and only two thirds of the water taken in is excreted, while normally an excess exists. Excretion of water by the urine is especially affected and amounts to only 26 per cent of the water intake. Perspiration is not compensatory and is abnormally diminished but not to such a high degree. EMERSON, Boston.

STUDIES ON ARTIFICIAL FEEDING OF INFANTS. DR. TADASHI SUZUKI, Series of Dissertations from Children's Clinic of the Kyoto Imperial University.

This study was undertaken with the purpose of determining, from a biologic point of view, the nutritive value of various dried milk preparations which appear on the Japanese market. Young albino rats were used for the major part of the experimental work, but unfortunately only single rats were used for each different regimen of feeding, so that the conclusions are not as convincing as they might be.

In the first group of experiments it was found that in rats, Borden's Malted Milk, Horlick's Malted Milk, and Kinomeal, (a Japanese malted milk preparation) were not as nourishing foods at Lactogen, dry milk, Klim and Dutch milk. Infants fed on the maltose-dextrin preparations did not gain well and showed symptoms of dyspepsia. The author's suggestion that such experiments indicate that dextrimaltose is not as easily digested as lactose or cane sugar seems unjustifiable as the various foods show differences other than in the type of sugar used.

Using preparations in which the fat, protein, and carbohydrate content resembled Kinomeal, the author concludes, from varying the type of carbohydrate, that in such a mixture cane sugar is better than dextrimaltose and dextrimaltose is better than lactose.

Admitting that the preparations such as Horlick's Malted Milk and Kinomeal are not satisfactory as infant foods, what factor in their composition is at fault? It was found that the addition of vitamin B in no way improved their nutritive value, but that with the addition of casein or albumin (about 7 per cent dry weight) good results were obtained. Small amounts of orange juice also improved the nutrition to some extent. Neither fat soluble "A" nor the ultraviolet rays seemed to have an appreciable effect.

LESLIE, Chicago.

Prenatal Conditions

AN EXPERIMENTAL STUDY CONCERNING THE ETIOLOGY OF CERTAIN DEFECTS OF THE LIMBS. HALSEY J. BAGGS, Internat. Clin. **4**:26, 1926.

By means of irradiation, strains of laboratory animals were produced which exhibited a strong tendency to the development of definite congenital defects. The following conclusions were reached after a study of 139 such animals with well marked abnormalities of the feet:

Clubfoot, congenital amputation, hypodactylism and syndactylism are anatomic abnormalities associated with a definite localized arrest in embryologic development.

This arrest may occur early or relatively late in prenatal life, and the variation in the time and extent of occurrence probably accounts for the variety of resulting adult conditions.

The arrest in development has been found to be associated first, apparently with a disturbed lymph circulation, and slightly later this condition is superseded by a localized extravasation of blood into the affected area and the formation of a blood-clot that acts as a disturbing factor and prevents the orderly, normal development of the limb.

The localized lesions vary in size to a great extent, and this seems to account for the diversification in the final defects in structure.

SMITH, Ogden, Utah.

Diseases of the New-Born

MALIGNANT NEUROBLASTOMA. BENJAMIN ROMAN, Bull. Buffalo Gen. Hosp. **4**:58, 1926.

An infant, aged 9 days, with jaundice and an enlarged liver, at necropsy revealed a tumor limited to the suprarenals and the liver. The latter was diffusely involved, its parenchyma almost completely replaced, and its form preserved. Histologically, the tumor showed the characteristic structure of a neuroblastoma, but nerve fibrils could not be demonstrated in it. The origin of the tumor was probably in the left suprarenal. The presence of icterus and the observation of bile in the gallbladder, in spite of almost total destruction of the liver cells, would lend support to the newer theories of bilirubin formation as based on hepatectomy experiments in dogs. AUTHOR'S SUMMARY.

TREATMENT OF MELENA NEONATORUM. R. HOLLANDER-PILPEL, Wien. klin. Wchnschr. **40**:589 (May 5) 1927.

The author reports the occurrence of massive hemorrhage from the gastrointestinal tract in an infant thirty-six hours after delivery. Symptoms of extreme exsanguination, including shock, quickly ensued. Bleeding continued in spite of injection of gelatin, horse serum, physiologic sodium chloride and drug stimulants. Thirty cubic centimeters of maternal blood was then injected into the femoral vein, with prompt improvement in the general condition and cessation of the hemorrhage. The author recommends that in cases of melena neonatorum blood transfusion be performed immediately, rather than following trial of less effective methods.

OLMSTED, Seattle.

Acute Infections

SCARLET FEVER STREPTOCOCCUS ANTITOXIN. TREATMENT OF SCARLET FEVER CASES. STEWART E. DOOLITTLE, Northwest Med. **26**:26 (Jan.) 1927.

Doolittle reports parallel series of treated and untreated patients from the Seattle City Isolation Hospital. In patients having severe and moderately severe cases who were given serum, defervescence occurred in about the same time as in the mild and moderately severe and untreated forms.

The patients who had been treated had a lessened incidence of complications, 18 per cent as compared to 23 per cent in spite of the greater severity. There were two deaths among 90 untreated patients, and none among 101 treated patients. The great value of the serum lies in the neutralization of the toxemia in the early stage of the disease. More antitoxin reactions were obtained with the unconcentrated serum.

SCOTT, Philadelphia.

RECENT ADVANCES IN THE ETIOLOGY, PROPHYLAXIS AND TREATMENT OF THE ACUTE EXANTHEMATA. J. D. ROLLESTON, Brit. J. Child. Dis. **24**:1 (Jan.-March) 1927.

Scarlet Fever.—The author discusses the claims of the three rival schools—the Italian School of Di Cristina and Caronia, who maintain that a diplococcus is the pathogenic agent, the American School of the Dicks, Dochez, Zingher, and Park who attribute the disease to *Streptococcus hemolyticus scarlatinae*, and the third school, that of Szontagh of Budapest, who maintains that scarlet fever

is not due to some definite organism, but depends on a variety of different causes. Rolleston concludes that "the streptococcus described by the Dicks has more claim than any other organism to be regarded as the causal agent of scarlet fever."

"As to the diagnostic value of the Dick reaction, my experience has been that it is too frequently negative in the first few days of the eruption and positive in convalescence to be a trustworthy guide." The Schultz-Charlton reaction has not, in the author's experience, been of much diagnostic value. He feels that scarlatinal toxin for purposes of immunization is still in the experimental stage "but is full of promise." He advocates the use of serum in the treatment of scarlet fever only in the severe forms.

Measles.—The author thinks that the diplococcus of Tunnicliff is more likely to be the causal organism of measles than any other hitherto described. He feels that immunization against measles, whether active or passive, is especially indicated in cases in which the disease is particularly dangerous, such as the ill nourished, rachitic children of the poorer classes.

Varicella, smallpox, erythema infectiosum, exanthema subitum, herpes fibrilis, and herpes zoster are briefly alluded to.

BACILLARY DYSENTERY IN ABERDEEN. ROBERT RICHARDS, Brit. J. Child. Dis. **24**:31 (Jan.-March) 1927.

The author cites a number of cases of dysentery in children and emphasizes two points in the diagnosis of this condition.

1. The macroscopic appearance of the stool, which is "like scrapings of flesh floating in raw meat juice."

2. The microscopic appearance of the stool, a smear of the feces showing a cellular exudate with abundance of polymorphonuclears and many "ghost" cells and macrophages.

Treatment by magnesium sulphate is almost specific, but must be ruthless, i. e., from 15 to 30 Gm. in water at least six times during the first day, with a daily diminishing number of doses as the symptoms begin to clear and with a single morning dose for several days after they have all cleared. A diet consisting of albumin water, beef tea, barley water, cocoa and weak, well sweetened tea is advocated while the mucus persists.

LANGMANN, New York.

IMMUNITY IN DIPHTHERIA. G. RUELLE, Rev. franç. de pediat. **2**:425, 1926.

The author reviews the subject of immunity in diphtheria, the passive immunity of the young infant, its disappearance and the development of an active immunity, even without clinical diphtheria, probably from an infection too slight to produce clinical symptoms. In testing for immunity, he finds that the antitoxic content of the blood does not always parallel the skin test reactions, nor do the skin tests always agree. Various factors may modify the reactions and may lead to false conclusions. In appreciating the significance of the Schick test, therefore, clinical judgment has a definite place.

LESLIE, Chicago.

ACTIVE IMMUNITY AGAINST DIPHTHERIA. WILHELM BAYER, Jahrb. f. Kinderh. **110**:273 (Nov.) 1925.

In spite of high antibody titer in the blood, infection with diphtheria is possible — frequently such cases have been reported. Also, animals that have been immunized may have a high immunity without antibodies in the serum.

Probably a vital antigen is necessary to produce an actual immunity. Bayer used a living diphtheria virus as described by Bohme and Riebold for immunization; from 0.05 to 0.005 cc. of the virus killed a guinea-pig when injected subcutaneously. eighty-seven infants, varying in age from 4 to 12 months, with positive Schick tests, were injected intracutaneously; the result was a red areola or pustule which involuted in five or six days. Sixty-nine of these children gave a negative Schick test from ten to twelve days after inoculation. Ten of those who were uninfluenced from ten to twelve days after the injection gave a negative reaction within a period of nine months. Twenty-nine of the previously negative reactions remained negative during a period of nine months.

EHRMANN, Chicago.

WHAT DO OPEN CUBICLES ACCOMPLISH IN THE CONTROL OF DROPLET INFECTION IN HOSPITALS FOR CHILDREN? ISMAR DZIALOSZYNSKI, Ztschr. f. Kinderh. **41**:685, 1927.

In the sick room without regulation of ventilation, coughing infants spread droplets to a distance of 4 or 5 meters. It is principally in the direction of the air current from the window to the door that the spreading of germs takes place. By corresponding currents, a spreading in the opposite direction may occur. The building of open cubicles does not really change anything, unless the partitions reach from floor to ceiling and unless the ventilation is controlled.

EMERSON, Boston.

Chronic Infections

FAVORABLE EVOLUTION IN CASES OF PULMONARY TUBERCULOSIS IN INFANCY. P. F. ARMAND DELILLE, J. VIBERT and P. PANNIER, Rev. franç. de pediat. **3**:1, 1927.

The authors report four cases of pulmonary tuberculosis in infants, in which there was a spontaneous clearing up of the active process. Roentgenograms are given showing various stages in the evolution. The authors conclude that the prognosis is not necessarily fatal, but because of the rarity of spontaneous cure, artificial pneumothorax should be used when possible.

LESLIE, Chicago.

TUBERCULIN REACTIONS WITH ESPECIAL CONSIDERATION OF TUBERCULIN LYMPHANGITIS. WALTER PFLÜGER, Ztschr. f. Kinderh. **41**:692, 1927.

On the basis of 268 graded Pirquet reactions in 100 children with tuberculosis of all kinds, the allergic condition of different forms of tuberculosis was tested. The highest allergy was shown by children with scrofula, tuberculosis of the bones and joints, closed pulmonary tuberculosis and active tuberculosis of the hilum and bronchial glands. Medium susceptibility to the reaction was found on the one hand in open pulmonary tuberculosis, and on the other in healed processes. Somewhat weaker reactions were shown by the pure intestinal and mesenteric gland tuberculosis. The severest allergy was found in cases showing severe cavernous pulmonary tuberculosis which was complicated by intestinal or laryngeal tuberculosis, by beginning meningitis, miliary dissemination or amyloid disease. The authors saw in numerous cases at the height of the reaction lymphangitic streaks in the neighborhood of the reaction, and they believe that the development of the lymphangitis is entirely

dependent on the strength of the reaction and of the concentration of the tuberculin solution used. It is a toxic inflammation of the lymph vessels caused by the tuberculin and is not a contamination of the tuberculin itself.

EMERSON, Boston.

Internal Diseases

BRITTLE BONES AND BLUE SCLERA. HEREDITARY HYPOPLASIA OF THE MESENCHYME. J. A. KEY, Arch. Surg. **13**:523, 1926.

A 12 year old girl complained that her bones were easily broken. She had had thirty-three fractures. The family history was significant. The mother had blue sclerae, was deaf and had had two fractures. The grandmother and great-grandmother on the mother's side were deaf and had blue sclerae. Three brothers and two sisters had blue sclerae and three of the five had multiple fractures. The condition is familial and is transmitted by affected parents. Only those children with blue sclera are subject to brittle bones and persons so affected are generally small in stature. The blue of the sclera results from an abnormal transparency of the sclerotic coat which permits the blue uvea to shine through. The deafness, which generally develops in adult life, is otosclerotic. Seventy per cent of persons with blue sclera have multiple fractures. These follow slight trauma and occur most frequently in childhood. The fractures are usually simple and occur generally in the shaft. It is characteristic that these fractures heal rapidly and well with little or no callous formation. Hypermotility of the joints, due to laxity of the fibrous supporting structures, leads to frequent sprains. The roentgenograms show the bone structure coarsened and the bone slender, and healed fractures frequently are not demonstrated. The bones are usually hard and brittle, honeycombed by large canals filled with vascular connective tissue and osteoblasts. The blood vessels, tendons, fascia and subcutaneous tissue are friable. The blood chemical observations are within normal limits. Idiopathic bone fragility may be classified thus: (1) hereditary form — hereditary hypoplasia of the mesenchyme; (2) nonhereditary osteogenesis imperfecta — (*a*) osteopsathyrosis with white sclera, (*b*) osteopsathyrosis with blue sclera; (3) osteosclerosis fragilis generalisata — marble bones.

N. ENZER.

INFANTILE ACRODYNIA. P. WORINGER, Rev. franç. de pediat. **2**:440, 1926.

This article includes an excellent review of the observations that have led to the conception of acrodynia as a definite clinical entity. Although no underlying anatomic lesion has been discovered to account for the many symptoms, the author feels that the various phenomena may all be explained by a functional disturbance of the vegetative nervous system. The apathy, depression, fatigue, the abundant perspiration and salivation, the moisture and the coldness of the extremities, and the urticaria may be accounted for on the basis of a vagotonia. The insomnia, tremor, hypertension and tachycardia fit in well with an overstimulation or derangement of the sympathetic system. Whether there is a toxin in the system that is elective for the vegetative nervous system or whether the glands of internal secretion are at fault is at best only a conjecture.

The condition rarely occurs in children over 8 years or under 6 months; its greatest incidence is in the winter and early spring, and it is usually accompanied by a pharyngitis. The disease is not fatal, death when it occurs

being caused by some intercurrent infection. In treatment, the author recommends life in the open air and sunlight, a varied food rich in vitamines and exposure of the whole body to ultraviolet rays. LESLIE, Chicago.

PATHOGENESIS OF THE PRESENT ANEMIAS IN CHILDREN. W. STEFKO, Monatschr. f. Kinderh. **35**:206, 1927.

This article is lengthy and somewhat abstruse. It discusses the histology of bone marrow, with various observations concerning embryology and the mechanism of the formation of the bone marrow elements. Of practical value to the pediatrician would be the author's observations that the severe hunger of the Russian children caused changes in the blood making system.

PAROXYSMAL CYANOSIS IN CONGENITAL HEART DISEASE. W. GRAVINGHOFF, Monatschr. f. Kinderh. **35**:237, 1927.

A case is reported, together with the roentgen-ray observations and the autopsy on a boy, aged 1½ years, who suffered from severe attacks of cyanosis. Pulmonary stenosis, with defect of the ventricular septum and transposition of the aorta, was found.

STATISTICS OF ANEMIAS IN CHILDREN. S. S. KAZNELSON, Monatschr. f. Kinderh. **35**:335, 1927.

In a statistical study, the author finds that from 1918 to 1925 the anemia in children seems increasing. This is true of the children of the small salaried man, of the laboring class and in the orphan asylum. In the asylum, the percentage of children with anemia was much greater than in the other classes. The author believes that the anemias come from three factors; namely, overworking of the school child, particularly as he approaches puberty, insufficient food and unfavorable living conditions. He is inclined to lay especial emphasis on overburdening of the child.

ORTHOSTATIC ACIDURIA. ERNST FAERBER and TELEMACHOS DEMETRIADES, Monatschr. f. Kinderh. **35**:346, 1927.

In studying children with chronic albuminuria, the authors noticed that when the child was in a recumbent position, the urine was alkaline or neutral, but became acid when the child assumed an erect posture. This interesting observation led them to conduct a more careful series of experiments on normal children. To their surprise, they found that the same rule holds true in normal children. In all children, when they are lying on their backs with legs elevated sufficiently to produce a sort of kyphosis, the urine becomes definitely alkaline. As soon as they assume an upright position, the reaction of the urine becomes acid.

Further observation of this interesting phenomenon showed that the urine obtained from the recumbent position was relatively large in quantity and of a low specific gravity, varying from 1.001 to 1.015, while the urine from the upright position was less in quantity and more concentrated, with a specific gravity of from 1.012 to 1.025. Thus, polyuria, alkalinity and dilution against oliguria, acidity and concentration were contrasted.

The next step in this interesting research was to determine whether the change in reaction from alkalinity to acidity was due to simple concentration

of the urine. To solve this, the authors gave the children sufficient amounts of water so that even in the standing position the urine was increased in amount and dilution. In spite of this, however, although oliguria and concentration did not now play any rôle; the reaction from the standing position remained acid. The reversal of these experiments confirmed the foregoing observations. When a child in an upright position with concentrated acid urine lay down, the urine became alkaline, but this change did not take place until after one or two hours had passed, showing that the processes causing acidity were active some time after the change of position.

While this process seems actually normal and a constant reaction in all children, it certainly has a definite relation to the subject of orthostatic albuminuria.

GERSTLEY, Chicago.

CLINICAL STUDY OF PNEUMONIA IN INFANTS. ERICH NASSAU, Ztschr. f. Kinderh. **41**:413, 1926.

In 1837, Seifert observed that bronchopneumonia in infants is different from that in adults; as does no other disease common to both, it differs in symptoms, types and treatment. The inflammation of the lungs is only a part of a disease that is general, and the extent of lung tissue involved, since the loss of respiratory surface is seldom great, is not the factor governing the outcome.

SYMPTOMS

There are two general symptoms complexes: the one based on disturbance of the parasympathetic system, and the other on disturbance of the heart and circulation.

1. The picture is one of pallor, weak pulse, low blood pressure, meteorism and associated flaccidity of the body musculature. Dyspnea is seldom seen.

2. By contrast, dyspnea occurs to the point of suffocation, secondary to weakness of the heart, which is the outstanding feature. The meteorism is due to the congestion of the splanchnic vessels, and a roentgen-ray examination of the heart shows it to be dilated.

There is no characteristic curve of fever.

Dyspnea and cyanosis and rapidity of respiration with activity of the alae nasi are not the direct results of the disease in the lung but are associated with disturbed functioning of the muscle and nervous systems. The action of the diaphragm, hindered by a flaccid belly wall, results in poor circulation in the intestines. Stimuli arising from the parasympathetic system cause congestion in the liver and portal vein, and lowering of the blood pressure by acting on the closing apparatus of the veins of the liver.

Barrel chest is a regular and early sign of inflammation of the lung, and is consequent to the rapidity of respiration which balloons out the sound portions of the tissue.

The counting of the pulse is not of the same value as extended observations of the blood pressure.

The loss of muscular tone is an unfavorable sign, especially in combination with a loss of tone of the smooth musculature resulting in meteorism. When meteorism suddenly disappears death follows.

Some cases are accompanied by an increase in myelocytes, and a continuance of the myelocytes over the fifth day is found only in cases with a fatal outcome. Plasma cells occur frequently and early and disappear with recovery;

they appear late in unfavorable cases. The reappearance of eosinophils, which are lacking in the beginning, is a favorable sign. The relation of leukocytosis and left shifting to the prognosis is presented diagramatically.

Leukocytosis	Left shifting +	Left shifting
	Prognosis: Severe but not fatal	Favorable
No leukocytosis	Prognosis: Bad	Doubtful

There are seven chief types of bronchopneumonia: (*a*) pulmonic; (*b*) cardiovascular; (*c*) atonic; (*d*) intestinal or alimentary; (*e*) meningeal and eclamptic; (*f*) toxic and septic.

(*a*) The pulmonic form is the one with the least involvement of other organs. Edema of the chest wall is an early and valuable sign. The loss of coughing is an unfavorable sign.

(*b*) In contrast to the pulmonic form the cardiovascular type is one of involvement of the heart and circulation, principally. The taking of food is hindered by dyspnea.

(*c*) The atonic form resembles the pulmonic and the cardiac forms; but from the beginning there is atony of the general musculature.

(*d*) The alimentary form is characterized by diarrhea and a loss of fluid and weight, appearing from two to four days after the onset but sometimes earlier, with resultant difficulty in diagnosis. There is marked meteorism.

(*e*) The meningeal form, with drowsiness lasting from five to seven days, and signs of meningismus confuse the picture. When convulsions appear, spasmophilia is always present.

(*f*) The toxic and septic form develops precipitately with restlessness, apprehension and collapse.

TREATMENT

The upright position of the infant is indicated except in cases in which there is a soft belly wall. In children with weak hearts and circulation, this position may lead to collapse. Packs are contraindicated as they interfere with respiration, especially in rachitic children with weak chest walls, and lead to the appearance of spasmophilia in children so disposed.

(*a*) In the pulmonic type, the infants do best if left alone.

(*b*) When the circulation is diminished and the nourishment of the heart cut down, just as there is no use whipping a tired horse, stimulants are contraindicated. The heart does its work with the help of glycogen obtained from the blood. The intramuscular injection of dextrose is the method of choice. It may be given in warm, 10 to 15 per cent solution, deeply into the gluteal muscles, from 30 to 50 cc. on each side. Sclerema-like changes may occur in the skin if the injections are often repeated, but they disappear in about three weeks. Other food is taken better if the infants are only half awake, a condition that is favored by the giving of veronal or phenobarbital. Stimulants should be given only for collapse.

(*c*) Dextrose may be given in the atonic type also. Daily intramuscular injections are given, usually about seven, until the tone of the muscle improves. Epinephrine is the best drug to use in that it removes the blockage set up in the veins of the liver, which holds the blood in the liver and abdominal veins.

(*d*) In the treatment of the alimentary form a dilemma is encountered. The modern practice is to give food in good amounts, and while this may lead to diarrhea, it builds up tissue and defensive power. Usually, food can be given

without danger of meteorism, but when food must be reduced the rule is to return to full nourishment as soon as possible.

(*e*) The treatment of the meningeal and eclamptic type is expectant. It is important to prevent spasmophilia from developing.

(*f*) The treatment of the toxic and septic type is of no avail.

The method of treating bronchopneumonia given in the foregoing aims, on the basis of functional diagnosis, to follow a functional theory suited to special conditions. The results of such treatment are encouraging. In 1924-1925, the mortality was 60 per cent. With this method of treatment, the recent mortality has been only 35.6 per cent.

AN ADDITION TO THE KNOWLEDGE OF ANEMIA IN CHILDHOOD. BERNHARD DE RUDDER and FRANZ WESENER, Ztschr. f. Kinderh. **41**:479, 1926.

A second child, exclusively breast-fed, became sick in his second month with a severe anemia. The blood showed excessive regeneration of red cells, marked anisocytosis, microcytosis, poikilocytosis, polychromatophilia and many normoblasts. The resistance of the red cells was greatly diminished, hemolysis beginning at 0.65 per cent. There was great enlargement of the spleen and liver. The first child in the family, according to the parents, had died with a disease of the same character. A diagnosis of familial hemolytic anemia was made, and the child was treated with all the usual therapeutic means without effect and died of influenza at the age of 4 months. A third child in the same family showed a picture which was the same as that of the second child in all the principal points, but this child was not breast-fed, showed enlargement of the spleen at 5½ months, which is unusually late, and so far has not had an anemia of the same degree of severity. She did show a head suggestive of Turmschädel, which has been noted before in the literature.

The autopsy of the second child revealed besides a great scarcity of red cells and red pulp, and much iron, great destruction of this tissue and a substitution of it with connective tissue. The sinuses were filled with a derivative of the proliferating endothelium and with marrow-like cells, which gave the oxydase reaction. The whole pulp was poor in cells, and there was marked general phagocytosis of red cells and no iron.

The clinical and pathologic observations do not correspond, since in hemolytic familial anemia the red pulp is rich in blood; there is rarely a phagocytosis, and no increase of connective tissue and little iron. Clinically, this was a case of familial hemolytic anemia but pathologically it was pseudoleukemic anemia.

A CASE OF PUBERTAS PRAECOX. SAMUEL GROSS, Ztschr. f. Kinderh. **41**:552, 1926.

A boy, aged 2½ years, showed excessive development of the genitalia and of the secondary sexual characteristics as well as a premature development of the whole body with early ossification of the epiphyses. His general development corresponded to that of a boy 5 or 6 years old, and his mental development, while above that of his age, did not correspond to that of his body. The stage of ossification was more that of a boy of 12 than of one of 2½ years. The father had had one healthy child by another wife, but by his second wife he had another child showing gigantism with excessive development of the genitals who died at the age of 22 months. A third child died with a congenital heart defect at the age of 6 months. EMERSON, Boston.

Nervous Diseases

PETIT MAL OR CARDIAC DISTURBANCE. G. A. SUTHERLAND, Brit. J. Child. Dis. **24**:16 (Jan.-March) 1927.

The author cites two cases with attacks simulating petit mal. The first patient, a girl of 3½ years, died and the autopsy showed an aneurysm of the pulmonary artery. The other, a boy, first seen at the age of 5 years, is still living at the age of 12.

As a result of study of these cases, the author makes the following suggestions:

1. In connection with attacks suggestive of petit mal, there may be present at these times a condition of tachycardia, with pulse rate more than 160 per minute, without obvious cardiac changes.

2. Such attacks may be characterized by loss of consciousness, screaming, giddiness, falling down, and sensations of pain in the chest or the abdomen.

3. The attack is usually sudden in onset, brief in duration, and sudden in cessation.

4. The symptoms of an attack are present only during the period of paroxysmal tachycardia and usually accompany the onset of the new cardiac rhythm.

5. An attack is often definitely induced by (*a*) excitement (nervous shock) or (*b*) by exertion (running, etc.).

6. While an organic basis of disease in the heart may be present, a similar condition of paroxysmal tachycardia with symptoms may occur in hearts organically sound.

MICROCEPHALY: POST-MORTEM REPORTS OF TEN CASES OF TRUE MICROCEPHALY. T. BRUSHFIELD and W. WYATT, Brit. J. Child. Dis. **24**:24 (Jan.-March) 1927.

The authors found that certain pathologic changes were more or less constant. In every case, the meninges showed signs of chronic inflammatory change. The dura mater was thickened and sometimes adherent to the pia arachnoid, and a degree of hydrocephalus was a common feature. The leptomeninges were thickened and opaque, with a gelatinous exudate extending over the cerebral hemispheres round the sylvian fissures to the base. In three instances, the vessels of the pia mater were intensely injected and appeared to be involved in an inflammation more recent and acute than that in the dura.

Underdevelopment of the cerebral hemispheres was a striking feature of most of the brains. The hypoplasia involved the entire cortex, but was always more pronounced in the parietal and occipital lobes, frequently mapping out the superficial distribution of the middle cerebral artery. Except in two cases, there was no numerical loss of convolutions, the difference being rather one of size and shape. Small shrunken and misshapen convolutions, known as microgyria, were found in each of the ten brains examined. In seven of the brains, gross lesions were present, such as internal hydrocephalus, porencephaly and developmental anomalies of the corpus callosum, etc. Six of the brains showed internal hydrocephalus. The cerebellum usually appeared large and well developed. The spinal cord was abnormally thin and underdeveloped, the pyramidal tracts being chiefly involved.

Microscopically, the cerebral cortex showed a definite paucity of neurons; in the precentral gyrus, for instance, there were areas almost devoid of healthy

pyramidal cells, while of the cells present many showed immaturity, imperfect development or signs of degeneration.

In regard to the theories put forward to account for the microcephaly, the authors maintain that no single theory is sufficient to account for the wide differences displayed in the brains which they examined, as they gave evidence not only of an inherent want of development, but also of antenatal disease and degeneration.

LANGMANN, New York.

POSTENCEPHALITIC SEQUELAE OF THE CEREBELLAR ATROPHY TYPE. R. DELBEKE and L. VAN BOGAERT, J. neurol. et psychiat. **26**:411 (July) 1926.

The authors describe a case of postencephalitic syndrome showing the features of cerebellar atrophy. The main symptoms were as follows: (1) disturbances of equilibrium, astasia-abasia, which were more pronounced than the disturbances of coordination; (2) asynergic signs, which were predominant; (3) symmetry of the disturbances, which were more marked in the lower extremities; (4) dysarthric changes of a special type (speech slow and with a guttural intonation). Intentional tremors or nystagmus were not elicited—the postural reflexes, however, were increased rather than diminished as is generally the case with lesions of the cerebellar tracts. The authors compare their case with those of olivopontocerebellar atrophy described by Dejerine and Thomas.

TIME OF ADAPTATION OF THE FEEBLE MINDED TO A NEW SURROUNDING. MEASURE AND ITS SIGNIFICANCE. E. DE GRIEFF, J. neurol. et psychiat. **26**:476 (Oct.) 1926.

The author studies the result of the heterofamilial placement of feebleminded children from the special standpoint of the time of adaptation to the new surroundings. The conclusion reached enables him to state that a rapid adaptation to the new surroundings is an unfavorable sign. One year at least should elapse before any definite evaluation can be expressed. The care of the feebleminded child by the family also needs an average of a year to assimilate the child. This is why attempts should be made to persuade the family to keep the patient for at least this length of time. The best period of life for trying the adaptation in a new surrounding is the period preceding puberty, and not later than the early period of this stage. Possibly winter has a favorable influence on the rapidity of adaptation.

FERRARO, New York.

DOUBLE PROGRESSIVE DEGENERATION OF THE LENTICULAR NUCLEUS. (MORBUS WILSON). BOUCKNER, Jahrb. f. Kinderh. **110**:284, 1925.

Three cases with autopsy reports are described. Each was characterized anatomically by a double degeneration of the lenticular nucleus in the region of the putamen. This was associated with a large nodular cirrhosis of the liver in two cases and once with a fatty infiltration and interstitial round cell infiltration.

Clinically, the disease is characterized by muscle rigidity, an apparently laughing face, slow movements and a negative Babinski sign.

ERHMANN, Chicago.

ALKALI AND CALCIUM CONTENT OF BLOOD SERUM IN TETANY. J. CSAPÓ and J. ISTVÁNCSICS, Jahrb. f. Kinderh. **115**:282, 1927.

Twelve infants with spasmophilia were studied. The following results were obtained: Calcium in milligrams per cent and base in cubic centimeters hundredth normal sodium hydroxid per hundred cubic centimeter of blood:

No.	Calcium	Base	Quotient Calcium Base
1	6.8	406	60
2	5.0	428	85
3	5.2	420	80
4	5.2	396	76
5	6.2	420	68
6	7.0	416	59
7	5.6	450	80
8	7.0	480	68
9	6.4	420	65
10	6.0	446	74
11	6.2	424	68
12	6.6	406	61

There is neither a compensated nor an uncompensated alkalosis in infantile tetany. The alkali-calcium quotient is higher in tetany; therefore, there is a relative excess of base. The explanation is a lowering of calcium content in the serum.

PETERMAN, Milwaukee.

THE NINHYDRIN REACTION. THE USE OF NINHYDRIN IN EXAMINATION OF THE SPINAL FLUID. HERBERT RAU, Ztschr. f. Kinderh. **41**:680, 1927.

The ninhydrin reaction proposed by Nobel in the examination of the spinal fluid shows a blue to red violet color, which is brought out by an increase in the albumin bodies and their broken down products. Its strength runs parallel to the total nitrogen content of the cerebrospinal fluid. If 1 cc. of spinal fluid is mixed with 3 drops of a 1 per cent ninhydrin solution and heated thirty seconds, the threshold value of the nitrogen content corresponds to an albumin concentration of 0.6 per cent.

EMERSON, Boston.

SIMPLE METHOD FOR DETERMINING THE GLOBULIN OF THE CEREBROSNINAL FLUID. I. NADOS-NIKITITS, Orvosi hetil. **71**:351, 1927.

Quantitative determination of globulin in the cerebrospinal fluid can be performed easily in small tubes prepared for this purpose. The following method is used: 2 cc. of cerebrospinal fluid is mixed with 2 cc. of saturated cold solution of ammonium sulphate and left to sediment from fifteen to eighteen hours in a test-tube 14 mm. in diameter. The sedimentation is continued in a specially prepared tube 5 mm. in diameter. The reading in percentages is done after from twelve to fourteen hours. The procedure can be shortened by centrifugalizing from five to ten minutes of sedimenting in the larger tube.

CHOLESTERIN CONTENT OF THE CEREBROSPINAL FLUID IN HEALTHY AND SICK CHILDREN. I. LÉVAY and J. MOSONYI, Orvosi hetil. **71**:432, 1927.

Bor's method for cholesterin determination was used with slight modification rendering it more sensitive. Cholesterin was found in the cerebrospinal fluid of healthy and sick infants and children in every case. The concentration of cholesterin in the cerebrospinal fluid is 1.70 mg. per hundred cubic centimeters in normal children; it is increased in microcephaly, idiocy, and hydrocephalus. It is increased in inflammatory processes of the brain and meninges.

ZENTAY, St. Louis.

Diseases of the Ear, Nose and Throat

OTORHINOLARYNGOLOGY IN INFANCY. DOUGLAS GUTHRIE, Arch. internat. de laryngol. otol. rhinol. **6**:129, 1927.

Three conferences were held at Paris during the clinic of the otorhinolaryngological and facial plastic surgeons. At the first conference the ear of the infant was considered. The usual anatomy was reviewed. Sections were shown demonstrating pneumatization of the mastoid fairly well instituted at the age of 2 years and well advanced at 6. Fifteen per cent of mastoids do not pneumatize, the bone remaining thickened; in case of suppuration intracranial complications are increased.

Otitis media in children under 2 years of age is of extreme frequency and importance. Much of the deafness of adult life may be traced to suppuration at this early age. Certain authorities believe that this early suppuration is the true cause of otosclerosis and nonpneumatization of the mastoid. Examination of a section of the ear at birth shows that the middle ear is filled with embryonic material, which may persist for some time and which may be subject to infection. Autopsies at Edinburgh showed that 80 per cent of nurslings had pus in the middle ear. Examination of the middle ear should be included in the physical examination of the infant — a procedure too often neglected. Many of the latent infections of infancy disappear spontaneously without being detected. Mastoiditis is a frequent complication of otitis, but usually responds to drainage. Seventy-eight per cent of suppurations of the middle ear and mastoid either cease spontaneously or are cured by operation. Ten per cent become chronic, and 7 per cent of the patients die of other causes. Of the chronic cases, 37 per cent are cured by conservative measures. Simple mastoid drainage gives good results in a large majority of instances; radical methods should be used as a last resort and are contraindicated in tuberculosis.

In the second conference the nose of infancy was the topic of discussion. The usual anatomy was reviewed, particularly the development of the sinuses. Special attention was called to the rounded contour of the infant's choana in comparison to the oval orifice of the adult. The choana becomes definitely oval at the age of 2 years, and at the age of 12 assumes the contour of the adult nose. The author believes that this shape of the infant's choana has much to do with the nasal obstruction that is so often found. The ethmoids are present at birth and are subject to infection. What was formerly considered a maxillary sinusitis in infancy is in reality an osteomyelitis of the superior maxilla caused by an infection of a dental bulb. Profuse discharge from the nose in early life may be due to foreign bodies, nasal diphtheria, sinus infection or syphilis. Dental, peridental and dentigenous cysts may be found. Deflection of the nasal septum may be found in the child, but its correction is usually difficult and not always satisfactory. Polyps are usually solitary and of maxillary origin.

The pharynx and larynx were considered in the third conference. Among the functions of the tonsils that were considered was that they may be hematopoietic organs, and also that they may be the source of a vaccine manufactured in the crypts. The indications for the removal were many and varied. Retropharyngeal abscesses may be due to tuberculosis of the cervical vertebrae or to an infection of the retropharyngeal ganglions. The latter are located in the prevertebral aponeurosis. On account of the higher location of the larynx in infancy, these abscesses cause more difficulty in respiration than at a later age. Of the many congenital malformations of the larynx, the most common

is the laryngeal stridor. This is functional, and usually disappears at the end of the second year. Spasm of the glottis is more frequently noted in children over 2 years of age. False croup may be observed. Papillomas, often multiple, are observed in early life. They may be removed by the direct method, but may recur.

ROTH, Kankakee.

A TYPICAL FIBROMA OF THE NASOPHARYNX IN A GIRL. JOSEF SCHLEGLMUENIG, Ztschr. f. Hals-, Nasen- u. Ohrenh. **17**:1 (Dec. 18) 1926.

The author describes a typical polyp of the nasopharynx in a girl, aged 13. It was the size of a hen's egg, with a broad base, which, under the microscope, showed signs of a hyaline degeneration. Coenen thinks that the basal fibromas are tumors of the skeleton, and that they develop from the embryonic chondrocranium.

BIOCHEMISTRY OF THE TONSILS. ERY LUESCHER, Ztschr. f. Hals-, Nasen- u. Ohrenh. **17**:60 (Dec. 18) 1926.

1. The method of Warburg permits one to make metabolic tests with a few milligrams of surviving tissue. Therefore it is especially adapted to clinical purposes in making microdeterminations.

2. The method applies to the investigation of the utiilzation of oxygen (breathing) and of carbohydrate metabolism of the tonsil. The results refer to the behavior in Ringer's solution.

3. The normal tonsil shows considerable utilization of oxygen and pronounced glycolysis (fermentation) takes place in them. The relation of fermentation to breathing is greater than in all other normal tissues.

4. This holds good also for adenoids. It seems to be a special quality of the germinal centers of peripheral lymph nodules.

5. Not only does the tissue act in this manner, but also the lymphocytes of the tonsil which wander to the surface through the epithelium.

6. The glycolytic effect is not present in salty extracts. Therefore it is not bound, in larger quantities, to extracellular colloidal material or to material in solution.

7. The hypertrophic tonsil differs from the normal tonsil by increased utilization of oxygen and more fermentation (there may be relatively more fermentation than oxygen). It presents a hyperfunction and dysfunction compared with the normal.

8. The thymus differs from peripheral lymph nodules by the absence of almost all fermentation. Lymph glands differ also in one person. Some show a relatively considerable fermentation, some almost none. The peripheral lymph nodules show great fermentation continuously, whereas the lymph glands show fermentation only at times.

9. Under certain circumstances, lymphocytes contain a substance of great glycolytic effect, which is bound fast to the cell.

10. Hypertrophic tonsils plainly show involution caused by age. Breathing and fermentation begin to decrease between the sixteenth and twentieth years. They decrease by about one half.

11. Sex has no influence on this metabolism.

12. Seasons seem to have an influence. The rate of metabolism is lower in spring and summer than in winter.

13. The total metabolism of the normal, and especially of the hypertrophic, tonsil is high, compared with that of other organs.

14. On account of their glycolytic quality, the penetrating lymphocytes are probably able to live anaerobically in the presence of hexoses. They keep the surface of the mucosa free from sugar.

(Hence the culture medium for bacteria is less favorable, and their virulence may become less.)

ACUTE ABSCESS OF THE TEMPORAL LOBE AFTER ACUTE OTITIS MEDIA. PAUL SAUER, Ztschr. f. Hals-, Nasen- u. Ohrenh. **17**:202 (Jan. 31) 1927.

A girl, aged 12, had suffered from pain in the right ear for seven weeks before she was admitted to the hospital. There was a discharge from the ear for several days before July 12, 1925, when the patient entered the clinic. Two days previously she had had fever and vomited. The temperature was 102.2 F.; the pulse rate, 128. After the child had been in the hospital for six days, a high temperature suddenly developed, with severe headache, a feeling of fatigue, vomiting and stiffness of the neck. A radical mastoid operation was performed on July 19, by Professor Preysing. The tympanum and antrum were surrounded by bone as hard as ivory and contained pus and granulations. On account of the presence of meningitis (stiffness of the neck, a positive Kernig sign, cloudy spinal fluid with numerous leukocytes), the dura of the middle and posterior cranial fossae was exposed, and an extradural abscess was found in the middle cranial fossa.

The patient was referred to the outpatient department on August 22 and readmitted on August 25, on account of severe headache, vomiting and fatigue. There were no meningeal symptoms and no nystagmus. Choked disks with hemorrhages into the retina were present. On September 12, the patient lost control of the sphincter. On September 19, the symptoms had increased. The choked disks became plainer (4 diopters on both sides); this was more pronounced on the left side. There was almost complete hemianopia on the left side. Optomotor nystagmus (cords) was absent to the left. Visual radiation was missing in the right eye. The observations of the eye proved the existence of an abscess of the right temporal lobe. Professor Preysing slowly evacuated 250 cc. of thin pus. A bent probe protected with moist cotton did not encounter any capsule. On Jan. 9, 1926, the patient was discharged well. A bacteriologic examination was not made.

In the great majority of cases, otitic abscesses of the brain are not caused by diseases of the mucous membrane in the cavities of the temporal bone, but by the diseased bone which almost invariably reaches to the dura. Experienced observers have reported forty cases of otitic abscess of the brain, in thirty-seven of which the bone was diseased. In one case the diseased bone did not reach to the dura, and in only two cases was it healthy. Manasse's "Acute Osteomyelitis of the Anterior Portion of the Skull in Acute Suppuration of the Accessory Cavities" illustrates well the path of infection in the class to which the case reported belongs, when he says: "The most pronounced microscopic

changes were found in the macroscopically intact bone. All vessel channels were so tightly filled with pus cells that the vessels could scarcely be recognized as such."

AMBERG, Detroit.

Diseases of the Skin

STUDIES IN URTICARIA: I. WHEAL PRODUCTION THROUGH INTERNAL CHANNELS. ABRAHAM WALZER and MATTHEW WALZER, Am. J. M. Sc. **173**:279, 1927.

After the injection into the skin of serum from a hypersensitive patient, the specifically offending food is given by mouth, whereupon a wheal may develop at the site of injection. This wheal apparently simulates a constitutional urticaria.

[ARCH. PATH.]

THE EFFECT OF ULTRAVIOLET RAYS ON THE REGENERATION PROCESS OF THE SKIN OF THE RABBIT. A. ABRIKOSSOFF, Verhandl. d. deutsch. path. Gesellsch. **21**:163, 1926.

The hyperplastic processes of the epidermis cells after radiation with ultraviolet rays were studied. The irradiated area becomes first warmer and redder than the adjacent skin, then the epithelium scales in delicate membranes, and finally, from 3 to 4 weeks after irradiation, an increased number of hairs appears in this area. The histologic examination reveals degenerative processes in the epidermis extending into the subcutaneous tissue, while the hair follicles are little affected. After the demarcation of the degenerated part by a wall of leukocytes a regenerative proliferation is observed. The number of the layers of the epithelium of the skin and of the hair follicles is increased. There is a production of giant hairs and of a larger number of lanugo hairs. The epithelization of ulcers is considerably hastened by irradiation with ultraviolet rays. The newly formed epithelial lining is thickened and sends solid epithelial processes into the subcutaneous tissue. New hairs are formed in these processes. After the repeated irradiation of an artificial ulcer the healing is protracted and epithelial cell proliferations are seen resembling in structure those present in basal cell cancer.

W. HUEPER.

FAMILIAL SYMMETRICAL GANGRENE WITH ONSET AFTER BIRTH. O. ULLRICH, Ztschr. f. Kinderh. **42**:272 (Nov.) 1926.

A slowly progressing ulcerative destruction of the end of the nose began shortly after birth in the case reported. The process appeared in the third month in a chronic progressive form on the hands and left knee, with swelling and local asphyxia, followed by a multiple symmetrical gangrene; several fingers became mummified and dropped off. Periungual ulcerations appeared on the remaining fingers. From the fifth month on there was a distinct tendency to heal, with radial scarification of the surface of the ulcers. Without paroxysmal disturbances of the circulation, without pain and with only a slight disturbance of the general condition, the picture suggested a mutilating leprosy. A fresh infection during the seventh month fanned the process and

resulted in a rapid development of new gangrenous areas on the penis and head. A special disposition of the tissue to necrosis was obviously the determining rôle. The same disease in an older child in the family confirmed the diagnosis of Raynaud's disease. The identity of type and of time of onset in the same family brought out strongly the hereditary disposition. Raynaud's gangrene appears more frequently in infancy than does the chronic progressive form in later life, and is without pain.

EMERSON, Boston.

Surgery and Orthopedics

PAPILLARY CYSTADENOMA OF THE OVARY IN A CHILD. JEROME L. HOLZMAN, Northwest Med. **26**:164 (March) 1927.

Holzman's patient was a child of 13, who complained of burning pains in the epigastrium and various gastro-intestinal symptoms. She had begun menstruation at 12 and had painful periods at forty-eight day intervals, lasting from ten to fourteen days. Between periods there was a thick white vaginal discharge. In the last attack the patient had lost 15 pounds (6.8 Kg.).

Examination showed tenderness and fluctuation low down in the right side of the abdomen. Fullness and increased resistance were felt in the right adnexa by rectal examination.

Operation showed free fluid in the abdomen with a cyst 2 inches (5 cm.) in diameter on each ovary. There were grape-like projections from the cysts, filling the pelvis and fixing the uterus. Radium and roentgen-ray treatment was followed for one year, and then at operation much of the cystadenomatous tissue was removed, leaving the uterus.

Holzman believes the prognosis to be uncertain as the benign papillary cystadenoma, while slow growing, has a marked tendency to become malignant.

SCOTT, Philadelphia.

ETIOLOGY OF GANGRENOUS APPENDICITIS. G. MICHEL, V. DELAVERGNE, E. ABEL, Arch. d. mal. de l'app. digestif. **17**:5, 1927.

The authors have studied by animal experimentation the bacterial flora of different forms of appendicitis. Their studies show that gangrenous forms of appendicitis, in accordance with the former knowledge, are the result of an infection with anaerobic bacteria. However, the feeble pathogenic action in experiments seems to show that the part played by these bacteria in appendicitis is only secondary, just as it is in other localizations of a similar infection. A preceding inflammatory process accompanied by circulatory disturbances is necessary for the growth of the bacteria, and therefore it seems that the cause of appendicitis in the last analysis is uniform. On this basis the further process develops either in the direction of suppuration or in the direction of a gangrene, depending on the extent of the circulatory disturbance that is the deciding factor about the intervention of anaerobic bacteria. These bacteria then change the aspect of the lesion through proteolysis and fetidity, which is characteristic of their presence. This may explain the good effects

of polyvalent antigangrenous serums. The mild pathogenic action of these bacteria shown in experiments explains that in spite of the fetidity of the pus and of the rather bad aspect of the lesion, the prognosis of this form of appendicitis is not bad if the appendectomy is performed at an early stage.

ZENTAY, St. Louis.

Miscellaneous

POSTURAL DEFECTS IN CHILDREN. HERBERT E. COE, Northwest Med., February, 1927.

Coe thinks that postural defects usually are caused by an inability of an atonic musculature to maintain the upright position. Faulty posture often results in a fatigue syndrome which presents numerous secondary symptoms relieved by development of weak muscle groups. Muscle development guided by a trained physiotherapist corrects faulty posture and improves the general condition.

SCOTT, Philadelphia.

Society Transactions

PEDIATRIC SECTION OF THE ACADEMY OF MEDICINE OF CLEVELAND

Fifth Quarterly Meeting, March 9, 1927

H. J. GERSTENBERGER, M.D., *in the Chair*

MUMPS MENINGITIS. DR. J. E. MCCLELLAND.

A boy, aged 9 years, developed headache, vomiting and cervical rigidity after an attack of mumps. The spinal fluid contained 800 cells, about 95 per cent of which were of the mononuclear type. There was only a trace of globulin. Improvement was noted immediately after the lumbar puncture, and in a few days there were only 20 cells in the fluid. At the present time he seems to be entirely normal.

SITUS INVERSUS VISCERUM TOTALIS. DR. L. R. BRIGMAN.

This condition was diagnosed by a roentgenogram taken when the patient was 3 weeks of age, because of suspected pneumonia. The infant had been examined previously by three different physicians, and in each instance the parents had been informed that the heart sounds were very weak.

INFLUENZAL MENINGITIS. DR. C. W. BURHANS.

The patient was a colored girl, aged 4 years. Especial emphasis was placed on the pleomorphism of the influenzal bacilli found in the spinal fluid.

BRONCHIECTASIS. DR. H. S. REICHLE.

Two patients were presented, and other cases that had been observed in the hospital were discussed. All gave a history of chronic cough following acute respiratory infections. Physical observations varied a great deal. Tuberculosis and foreign bodies in the lung had to be excluded.

AN UNUSUAL CASE OF CHRONIC DYSENTERY. DR. E. R. BROOKS.

A girl, aged 10, had been suffering from diarrhea for nearly two years. Intermittent fever had been present and marked emaciation had occurred. Proctoscopic examination showed an inflammation of the lower bowel but no ulceration. Recently she had improved while in the hospital on a high protein diet to which fresh strawberries had been added. Several blood transfusions had been given.

DISCUSSION

DR. GERSTENBERGER: I believe that this is a case of sprue, which many think is primarily a metabolic disturbance with a superimposed infection.

CHRONIC CALCIFYING PACHYMENINGITIS: A PATHOLOGICAL SPECIMEN. DR. H. GOLDBLATT.

A brief resumé of this patient's history and physical observations was presented by Dr. W. B. Taggart. A colored girl, aged 4 years, had been under

observation for the past three years. At various times a mononucleosis had been found in the spinal fluid. A hydrocephalus had developed but no evidence of an irritative cerebral lesion. Optic atrophy had been present for some time.

DISCUSSION

DR. GERSTENBERGER: This is one of the few cases of true external hydrocephalus.

DR. E. C. CUTLER: I had considered it clinically as an instance of an inflammation of the ventricles without cortical involvement.

ASTHMA DUE TO TUBERCULOSIS OF THE HILUM. DR. J. I. HARTMAN.

A patient, aged 6, years, was admitted to the hospital with symptoms of acute bronchial asthma. No improvement followed the subcutaneous administration of epinephrine. The roentgenogram showed a large mass surrounding the hilum. The tuberculin test was strongly positive.

PARINAUD'S CONJUNCTIVITIS. DR. J. D. PILCHER.

This is a vegetative inflammation of the palpebral conjunctiva with enlargement of the preauricular gland on the same side. The patient had a positive tuberculin test.

DISCUSSION

DR. M. P. MOTTO discussed the case from the standpoint of the ophthalmologist.

NEPHROSIS WITH PNEUMOCOCCIC PERITONITIS. DR. J. D. NOURSE.

The patient gave a history of having recurrent attacks of edema and albuminuria. Recently a large tumor had been discovered in the lower part of the abdomen. This was incised and a large quantity of pus containing type IV pneumococcus was obtained. The other symptoms disappeared following the operation, and the boy is now ready for discharge.

PAROXYSMAL HEMOGLOBINURIA. DR. H. J. GERSTENBERGER.

A girl, aged 10, gave a strongly positive Wassermann reaction. The blood of the parents showed the same reaction, but an older brother gave a negative test. Attacks of hemoglobinuria could be brought on by chilling the patient's feet in cold water. Chilling a mixture of her serum and cells in a test tube produced a definite hemolysis after warming.

Sixth Quarterly Meeting, May 4, 1927

H. J. GERSTENBERGER, M.D., *in the Chair*

COMPLETE OCCLUSION OF THE DUODENUM BY TRANSVERSE MEMBRANE. DR. J. A. GARVIN.

The infant died on the fifth day after birth, presenting the signs of intestinal obstruction. This anomaly constitutes about one fourth of all the conditions causing congenital obstruction of the gastro-intestinal tract.

DEXTROCARDIA WITH PULMONARY ARTERY ARISING FROM THE AORTA. DR. J. A. GARVIN.

The heart was on the right side and showed only one auricle and one ventricle. The two pulmonary arteries arose symmetrically from the thoracic aorta. The pulmonary veins emptied into the superior vena cava, and no inferior vena cava was found. There was also a congenital absence of the spleen. So far Dr. Garvin has been unable to find in the literature any description of an anomaly like the one here described.

CONGENITAL HEART BLOCK IN AN INFANT AGED 13 MONTHS. DR. J. H. DAVIS.

The condition was probably due to a lesion of the conduction bundle, associated with a patent interventricular septum. The only complaint was that the infant did not gain in weight at the normal rate. There was no cyanosis or clubbing of the fingers. The electrocardiogram showed an auricular rate of 125 and a ventricular rate of 45. The ventricular rate was unaffected by the oral administration of atropine. This is the sixteenth case of congenital heart block to be reported.

UNILATERAL PARALYSIS OF THE DIAPHRAGM AS AN OBSTETRICAL INJURY. DR. J. W. EPSTEIN.

The right side of the diaphragm was involved following an injury to the brachial plexus during birth. The diaphragm on the right was at the level of the fifth interspace, while on the left it was at the tenth interspace. The right lung was completely atelectatic. Dr. Epstein has observed this child for three years, and there has been no improvement in the paralysis. The patient's development has been somewhat retarded, and it has been hindered by several attacks of bronchopneumonia of the affected lung. The first report of a similar condition appeared in 1921.

SELF-SELECTED DIETS OF NEWLY WEANED INFANTS. DR. CLARA DAVIS.

Two normal infants were the subjects of these observations. Immediately after weaning they were allowed to select their own food from a variety of dishes placed before them on a tray. Both sweet and acid milk were offered. Careful records were kept of the amounts and the types of foods eaten for a period of several months. Both infants gained at a slightly more rapid rate than the average normal infant, and they remained entirely free from any gastro-intestinal disturbances.

AMERICAN PEDIATRIC SOCIETY

Thirty-Ninth Annual Meeting, May 12, 13 and 14, 1927

The members of the association sailed from Washington, D. C., May 12, at 2 p. m. on the S. S. *Southland*, of the Norfolk and Washington Steamboat Company.

First Session, Thursday Evening, May 12

The first scientific session was called to order by the President, Dr. Isaac A. Abt, Chicago, at 8:00 p. m.

PRESIDENTIAL ADDRESS. THE INFLUENCE OF PATHOLOGY ON THE DEVELOPMENT OF PEDIATRICS. DR. ISAAC A. ABT.

This article appears in full in this issue.

BACTERIOLOGICAL DIAGNOSIS OF LUNG TUBERCULOSIS IN INFANTS BY EXAMINATION OF THE GASTRIC CONTENTS. DR. P. F. ARMAND-DELILLE, Paris, France.

In infants with pulmonary tuberculosis, who swallow the sputum, finding of the tubercle bacillus is difficult. Examination of the stool or of material coughed up and caught on a swalb is not satisfactory.

The following method has been devised: About 80 cc. of tepid water is introduced into the stomach by tube and withdrawn. If typical tuberculous material is present, it is examined at once. If not, the stomach contents is divided into four parts and is centrifugalized, the supernatant fluid poured off and the remainder placed in a porcelain dish with 30 cc. of water and 10 drops of normal sodium hydroxide is added, heated for ten minutes with 50 cc. of water added slowly. A little alcohol is then added if the specific gravity is above 1.004. The four tubes are again centrifugalized for forty-five minutes and the sediment stained by the Ziehl-Nielsen method.

In sixty-two patients examined by the usual methods, only 10 per cent showed positive results, while in 110 cases in which this method was used 31 per cent gave positive results. In many instances doubtful diagnoses were definitely confirmed by this means even though the roentgenogram was not at all determinative.

FIVE YEARS' EXPERIENCE WITH THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY IN CHILDHOOD. DR. HENRY F. HELMHOLZ.

One hundred and forty-four chilren have been treated with the ketogenic diet. Twelve of these suffered from symptomatic epilepsy complicating encephalitis and cerebral palsy, and were treated for the most part at the parents' request. Enough improvement has occurred in this group to demonstrate that the treatment is worth a trial, even though the percentage of cures is decidedly lower than in cases of idiopathic epilepsy.

Of the 132 cases of idiopathic epilepsy, seventeen were observed in the last six months and are therefore not included in the determination of results. Twenty-four cases are unclassified, because the information obtainable was not clear-cut enough to justify classification.

Ninety-one patients have been on the diet long enough to give a definite idea of the effect of ketosis on the number and severity of convulsive seizures. The diet did not seem to have produced a therapeutic effect in forty-two (46 per cent) of these ninety-one patients. Some of the children made temporary progress, but it was soon evident that the diet alone would not control the seizures.

Forty-nine patients (54 per cent) were definitely benefited by the diet. In ten patients, whose ketosis was constant, the attacks were reduced in number and the intervals between them were lengthened. Ten patients are without attacks when in a state of ketosis, but there are constant breaks in diet.

Eight patients have been free from attacks for from six to twelve months. Three patients were free from attacks for more than a year but when the diet was modified, attacks again appeared, but resumption of the former diet once more controlled the attacks.

Eighteen patients have been free from attacks for from one to four years. Twelve of these are now on a normal diet and are free from attacks. It is, of

course, possible that some of the latter may relapse as did the three patients just mentioned, but there is every likelihood that resumption of the diet would again control the attacks.

DISCUSSION

Dr. Fritz B. Talbot, Boston: I think the pediatric world should feel a deep debt of gratitude to Dr. Helmholz for the fine work that has been done on the ketogenic diet and for drawing our attention to this method of treatment.

We have been carrying on this type of work, and it is very curious that we have also in our series of cases obtained complete relief of symptoms for varying lengths of time in 30 per cent of our cases.

In the tables that Dr. Helmholz showed, two of the columns gave the relations of carbohydrate and protein to one another. I have found that when the relation of fat to the combined carbohydrate and protein was 1½ : 1, there would be no ketosis and when the relation was 2 : 1, some ketosis would always be present. I notice that ketosis did not appear in Dr. Helmholz's two cases until he got the relationship as high as 2½ : 1. I wonder where the discrepancy is between his figures and ours?

I should like to ask Dr. Helmholz, what he means by a severe ketosis? From my point of view I mean a severe ketosis when I get what I call a four plus reaction of the urine, and I mean by that a deep purple color to the sodium nitro-prusside test.

When other members of the family contract colds, these children do not become sick, as a rule. My experience suggests that possibly the state of ketosis may influence in some way the infectibility of these children. This winter I had one child with a severe ketosis, who had double pneumonia which lasted three days. Another child developed scarlet fever. Both children recovered. Neither had a return of the attacks during these illnesses. Several years ago, Stanley Cobb drew attention to the fact that the epileptiform attacks usually disappear during an acute infection.

Dr. Henry Heiman, New York: Will Dr. Helmholz give us an explanation of the rationale of his treatment? Is it due to a diminished excitability of the nervous system of the ketotic child, or has he any other theory to explain the effectual result of his treatment?

Dr. Charles Hendee Smith, New York: I have a child under observation at present that is interesting in this connection. If this little girl breathes deeply twenty-five times, she has an attack of petit mal due to the relative alkalosis induced by hyperpnea. It is useful in demonstrating the nature of these attacks to students and perhaps has a practical application. I found that by giving her alkalis she would have the attack of petit mal after fifteen deep breaths, and that by giving her acids it would take place after thirty-five or forty breaths. I do not know whether this is a constant phenomenon in all cases of petit mal. It might be a means of encouraging the parents of these children to continue the treatment, if one could demonstrate that the induced ketosis made it more difficult to bring on an attack by deep breathing.

Dr. Samuel W. Clausen, Rochester, N. Y.: Dr. McQuarrie at Rochester has taken occasion to measure the output of acetone bodies in two-hourly periods during the day in patients receiving a ketogenic diet. He finds that there is a different output at these periods, that the maximum output occurs in the afternoon and that the minimum output, which approaches practically the normal one, occurs in the morning hours. The same curve is shown in normal children and in cases of epilepsy. When these patients are put on a

ketogenic diet their convulsions always occur in the morning hours, at the period when no acetone bodies are being excreted. When such a patient, however, who has been on a ketogenic diet is given dextrose and insulin, convulsions are liable to occur immediately.

I should be interested to know whether Dr. Helmholz has observed this same phenomenon?

Dr. Howard Childs Carpenter, Philadelphia: Is it a correct observation that a patient on a diet producing ketosis with the correct ratio of fat, carbohydrate and protein at each meal, will in all probability have fewer convulsions than if this ratio is not maintained for each meal, but only for each twenty-four hour period?

Dr. Helmholz (closing): In the thirty-seven patients reported from our clinic in 1925 by Pittman, nineteen were free from attacks when dismissed and of these ten are at present free; this brings the percentage down close to 30.

I consider it necessary to have a ketosis sufficient to produce a positive Gerhardt test (the definite Burgundy red) in the urine. Until this test becomes positive we continue to decrease the amount of carbohydrate.

I think that Dr. Talbot brought out an important point—the ease with which children seem to take the diet. The only difficulty seems to be at the beginning. I have not seen any difficulty with the diet in any of the youngsters that have gone through acute illnesses; if one attempts to put them into a state of ketosis rapidly one is likely to have serious digestive disturbance. Later on, with the onset of any acute illness, they seem to be little affected.

I do not know why this diet acts beneficially. I hope to get started during the next year on this question, but there is a great deal about fat metabolism that is not known at the present time.

In regard to the morning attacks, I have not taken particular account of that factor. Regarding Dr. Carpenter's question, I think that it is important that meals be balanced so that the youngster will not get an excessive amount of carbohydrate in one meal and an excessive amount of fat in another, because we are aiming to maintain this balance during the entire twenty-four hour period.

Heat Regulation in Premature Infants. Dr. Fritz B. Talbot, Alice J. Dalrymple and Velma Bates.

The inability of the premature infant to regulate its body temperature is generally recognized, but to my knowledge there is little data to substantiate the assumption. I recently had an opportunity to study the matter at the Infants' and Children's Hospital, in which the rooms for premature infants are equipped with a modern heating, ventilating, and air conditioning installation which makes it possible to keep the rooms at any desired temperature and humidity, regardless of outdoor weather.

The procedure was as follows: Four infants were chosen, two of which were premature, of a fetal age of about 7½ months. The other two infants were normal and were used as controls. In one series of observations, the temperature of the room was increased from the customary level of 80 to 90 F. In another series, the temperature was decreased from 80 to 64 F. The relative humidity was maintained at 30 per cent in both series. All other conditions, such as clothing, feeding, manner of exposure, etc., were kept unaltered. The reactions of the infants to the changes in the environmental temperature were studied by observing the changes in the rectal and skin temperatures.

The comparative reactions of normal and premature infants to cooler and warmer surroundings are summarized in the following table:

Effect of Cooling the Room 9 Degrees C.

	Exposure, two and one-half hours		
		Skin Temperature	
	Rectal	Trunk	Extremities
Normal infant.....	—0.0 C.	—1.3 C.	—3.8 C.
Premature infant.....	—0.2 C.	—3.6 C.	—6.3 C.

Effect of Warming the Room 5.5 Degrees C.

	Exposure, two hours		
Normal infant.....	+0.0 C.	+2.5 C.	+2.4 C.
Premature infant.....	+0.5 C.	+4.6 C.	+5.2 C.

The reactions to either heat or cold are much more pronounced in the premature than in the normal infant. This fact seems to indicate that the heat regulating mechanism of the premature infant is not functioning as efficiently as is that of the infant who reaches term.

Another interesting observation is the readiness with which the normal infants perspired in the conditions of high temperature as compared with the delayed perspiration of the premature infants. The normal infants began to perspire when the difference in temperature between the skin of the trunk and the rectum was from 1.3 to 2 C. The premature infants did not commence to perspire until this difference was about 0.6 C. Apparently, this is evidence of undeveloped activity of the sweat glands.

THE STABILIZATION OF THE BODY TEMPERATURE IN PREMATURE INFANTS. DR. K. D. BLACKFAN and C. P. YAGLOU.

If the fluctuations in body temperature in premature infants are dependent chiefly on variations in the environmental temperature, the problem of heat regulation should be comparatively simple. After securing uniform and constant atmospheric conditions by an "air conditioning system" designed by Mr. Drinker and Mr. Yaglou, of the School of Public Health, and installed in two small rooms of the Infants' Hospital, I was in position to study the problem of the stablization of body temperature in premature infants.

The air conditioning system makes it possible to adjust automatically the environmental temperature and humidity at any desired level. The principle of operation is as follows: Fresh air drawn from out-of-doors is "conditioned" in the apparatus and is then forced through metal ducts into the rooms of the premature infants. The vitiated air is withdrawn to the outside or, if desired, part or all of the air can be returned and reconditioned. The advantage of the equipment is that the air can be warmed and humidified in winter and cooled and dehumidified in summer.

In seeking the optimum conditions for the stabilization of the body temperature at 98.6 F., we found that the optimum environmental temperature depended considerably on the humidity of the air. From our observations, it was apparent that the body temperature could be stabilized at 98.6 or 98.7 F. with a low humidity and a high temperature or with a high humidity and a low

temperature. Two conditions were found suitable: 80 F., dry bulb temperature and 30 per cent relative humidity and 77 F. dry bulb temperature and 65 per cent relatively humidity. We may speak of these as thermo-equivalent values, as under both conditions the body temperature became stabilized at the desired level with a minimum degree of fluctuation. Infants under 2½ pounds (1.1 Kg.), however, may often require a higher environmental temperature.

During the past summer, twenty-seven infants were kept in a uniform environment of 77 F. and 65 per cent relatively humidity for five months, but we have not as yet attempted to place a comparable number of infants in a continuous environment of 80 F. and 30 per cent relative humidity. It is conceivable that injurious disturbances in water metabolism might result if premature infants were kept over a long period of time in an atmosphere of such relatively low humidity. Further information is being collected by changing the room conditions each week from 80 F. and 30 per cent relative humidity to 77 F. and 65 per cent relative humidity, but until more data have been obtained, we are not justified in concluding which of the two conditions is more ideal. However, as a result of our studies, we may conclude that temperature and humidity are two inseparable factors that should be taken into consideration when attempting to stabilize the body temperature of premature infants. The air conditioning system has proved to be a useful and practical equipment in the group care of premature infants.

PREMATURE INFANTS: A REPORT OF TWO HUNDRED AND SIXTY-SIX CONSECUTIVE CASES. DR. JULIUS H. HESS and DR. I. M. CHAMBERLAIN.

The station at Michael Reese Hospital has a capacity for the care of twenty infants. There are three rooms, one of which is devoted to normal infants and one to infected infants and the third for infants being prepared for removal to their homes.

About 75 per cent of the infants cared for have received free service at the request of physicians, midwives or nursing organizations who have referred the patients to the hospital.

So far as practical, the hospital sends its small, electrically heated hand ambulance with an intern and nurse to bring the infant to the station.

The equipment of the station is not elaborate, consisting of individual electrically heated water-jacketed beds, heated dressing tables, hygrometers, quartz lamp and time clock.

Human milk is the diet used for all infants during the first days or weeks in the department as their needs may indicate.

The station is under the care of a graduate nurse who has under her direction the needed number of women trained for this special work.

The mother is encouraged through the efforts of the social department to keep up her supply of breast milk.

In preparation for the infants' return to their homes, the social service department visits the home to which the babies are to go, at regular intervals, for the purpose of instructing the mother in the preparation of feedings and the required hygienic care of the infants.

A special clinic for graduated infants is conducted at the hospital for the ones who are likely to be neglected in their homes unless properly supervised.

The station has had a steady growth since it was opened in 1922. During its first year, nineteen infants were received; in 1923, twenty-eight; in 1924, forty-seven; in 1925, sixty-six, and in 1926, one hundred and six. In our series of 266 cases, 138, 51.9 per cent of the infants were discharged from the hospital,

in most instances directly to their homes. Excluding the fifty-four infants who died in the first twenty-four hours, 66.9 per cent survived. Immaturity and its associated pathologic conditions, refrigeration and neglect, were the common causes of death in those dying in the first twenty-four hours.

Autopsies were performed in seventy-nine cases.

Of the ninety-three infants followed in our clinic for infants graduated from the station, seven died; five had pneumonia. Two of these developed pneumonia during the course of measles. Seventeen of the infants have had measles and nine, pertussis. Respiratory infections have been little more frequent than in full-term infants. Two have had tonsillectomy performed without any unusual complications. The one syphilitic infant followed had a negative Wassermann reaction by the nineteenth month. While many of the infants showed minor, and a few moderate, degrees of rickets, only a small number have developed marked manifestations. This was believed to be due to the fact that cod liver oil and quartz light therapy were introduced when the infants were 2 or 3 weeks of age. There were no cases of rickets requiring mechanical appliances or surgical intervention to correct deformities.

Megacephalus, while occasionally seen, disappeared early, due it was thought, to the early addition of cod liver oil to the diet together with daily exposure to the ultraviolet ray. Active signs of tetany did not develop in any of the infants of the series.

Teething had been delayed as would be expected; however, nineteen of the infants had one or more teeth during the seventh month. As a group, by the eighteenth to the twenty-fourth month, they resembled closely in physical and mental development full-term infants. Apparently, there were no mental defectives in the series. Nature had wisely removed those not fitted to survive.

DISCUSSION OF PAPERS OF DRS. TALBOT, DALRYMPLE AND BATES, DRS. BLACKFAN AND YAGLOU AND DRS. HESS AND CHAMBERLAIN

Dr. Henry J. Gerstenberger, Cleveland, Ohio: A number of years ago, Dr. Huntington reported on the basis of a study of about six million deaths that occurred in different parts of the world that, in his opinion, it seemed better for man to live in an atmosphere with a low temperature and relatively high humidity rather than in one with a high temperature and relatively low humidity.

I myself have been uncomfortable in the winter time in the modern homes, offices, schools and public halls, in which no humidifying apparatus has existed in connection with the heating apparatus. The air becomes dry and so do the nasal and pharyngeal mucous membranes, and it seems that colds develop more rapidly under those circumstances. On the basis of Huntington's conclusions and our own personal experiences, when we equipped the new Babies and Children's Hospital in Cleveland, we had put in each ward a humidifying apparatus in order to enable us to increase the humidity. We have now attempted for two winters to keep each ward around 65 degrees and the humidity around 65, also. To strangers, the wards have seemed cool, and they have experienced a chilly sensation, but the doctors and nurses working in the wards have been comfortable, and on the whole they much prefer the change to the old condition.

When Dr. Truby King was in this country in 1917, he complained bitterly to me about the heating and dryness of our homes and said that in his country, New Zealand, the houses were kept at about 65 degrees, as Huntington had suggested.

I should like to ask what Dr. Hess did to prevent his premature infants from getting rickets?

Dr. L. E. LaFétra, New York: With regard to the advantage of having a higher temperature with lower humidity, or a lower temperature with higher humidity, I reported to this society several years ago an experience that we had had at Bellevue Hospital. At that time we had no method of regulating accurately the humidity, nor the money for putting in such elaborate apparatus as Dr. Blackfan and others have at their disposal. But, in order to maintain the temperature of the infants at 98.5 or 99 we found that, using the ordinary air of the ward, it was necessary to keep the temperature of the room somewhere between 85 and 90 degrees. We found that the infant's lips became dry and cracked and that they did not gain in weight as well as they should, notwithstanding breast feeding; then we gradually began to humidify the air by simply keeping a pan of water on an electric heater. By making the air in the room moist in that way, we were able to maintain the temperatures of the infants at normal, 98.5 or 99, with a room temperature between 76 and 80 F. The infants' lips did not become dry; they did not get infections of the nose and throat, and everything went on better. Moreover, the nurses who had to be constantly in the room were much more comfortable.

Dr. Carpenter: In reference to the temperature and humidity of the room, is it not true that in the open ward an additional factor has to be taken into consideration, namely, the activity of the air?

Dr. L. T. Royster, University, Va.: It is with great hesitancy that I discuss this question at all, because I do not know the handling of premature infants from the standpoint that the three speakers have discussed, but having practiced private pediatrics for many years and having had to attend premature infants in all classes and conditions of homes far more frequently than I have had opportunity to see them in a hospital—let alone the well regulated departments for premature infants—I feel that these gentlemen have done well. Trusting to my memory alone, I think that even under all those conditions my own series measures up fairly well with the rest of the statistics. I agree with what has been said about the humidity from my limited observation, though all my premature infants at the University of Virginia Hospital have been handled in a nursery with normal infants, and we have used no special apparatus whatever beyond the premature jacket. I have relatively little difficulty in keeping the rectal temperature between 98 and 99. Rarely does it go above that and almost never below after it is once gotten up, and without any apparatus at all.

One word about feeding these infants. I am not always able to get breast milk because of various conditions, and I found on comparing notes with a number of physicians throughout the country that in a certain number of cases in which breast milk was used exclusively, some premature infants did not gain well until cow's milk was added to the breast milk, so that in my last fifty cases of premature infants over the past two years I have made some definite experiments and have secured remarkable results with whole milk, acidified usually with lactic acid. In my experience they not only did as well so far as growth in length and weight were concerned as they did with the mother's milk, but very frequently they did far better. I know that is iconoclastic, and yet it is my own experience. I do not hesitate to say that in my last fifty infants, not over one third of which were on breast milk, the others being on artificial feeding entirely, I have had children that developed about like those Dr. Hess has just spoken of, reaching the weight of a normal baby about the same time that his did, and in many instances they have gone beyond

that on whole acidified milk exclusively. I have no hesitancy in saying that I am about as able to save a premature infant on whole milk acidified as I am on breast milk.

Dr. Warren R. Sisson, Boston, Mass.: We have had considerable experience at the Boston Lying-In Hospital, where we have about seventy-five to one hundred premature births a year. I should like to mention a few things that agree remarkably with Dr. Hess' experience. This year, we lost about 46 per cent of seventy-six infants, that is, including all that lived one hour or more.

I am interested in the cause of death in the cases that Dr. Hess has reported. It seems to me that in the group of atelectasis there is some question as to what atelectasis is. I should like to know what he means by that term. I should think atelectasis was perhaps the end result rather than the primary cause of death.

Furthermore, as to the infants who die with intracranial hemorrhage, we have thought the cause in a certain number of cases was probably an anoxemia, which is a possible cause of hemorrhage.

With regard to rickets, we do not use treatments with light or oil and have essentially no rickets.

Dr. Louis C. Schroeder, New York: I should like to ask Dr. Blackfan whether he considered the cubic air content of the rooms? I have wondered what relation his figures would have to the cubic air content he allowed the child. I believe that before the diagnosis of atelectasis is made, one should be certain there has been no twisting of the cord, or other cause of intra-uterine asphyxia.

Dr. Smith: In most hospitals, the infant lies in a hospital "flannel" shirt, a band and a hospital nightgown, split up the back. He kicks the clothing off and loses heat more quickly than he can replace it. For the past year in Bellevue and the Sloane Hospital, the infants have been pinned in bags constantly. In fact, the dress has been discarded. The infant is merely put in a bag made of a single fold of material and pinned in so that he is in an atmosphere that he keeps warm with his own heat because there is less radiation. We have had a smaller number of subnormal temperatures and fewer chilled infants since using this plan. An elaborate mechanism like that described in the paper is not necessary for the average infant, but of course for the premature infant it is highly desirable. If the heat is kept where it belongs, inside the clothing and bedding instead of being dissipated through improper clothing and an improperly made bed, the result will be a warm infant.

Dr. Hess: Did Dr. Blackfan make any studies of the infants' temperatures during the hot days of summer when there is naturally a high temperature and a humidity approximating 30 in the wards, and the other extreme, when there is a low temperature and a high humidity? If so, what effect did this have on the infant's temperature?

Dr. Blackfan, (closing): With regard to Dr. Carpenter's question, I do feel that the air velocity has a great deal to do with the comfort of the individual, the three factors being temperature, humidity and air velocity. The variation is considerable, depending on whether one has a low temperature and humidity and no air stirring, or whether he has a high temperature and humidity, with a great deal of air stirring.

As to Dr. Schroeder's question, we have two rooms; in the first there are five and in the second six infants. When the rooms are fully occupied, there are 300 cubic feet of air for each baby.

I do not understand Dr. Hess' question. If he means studies on premature infants, we have made analyzed studies of that kind, taking into consideration the temperature of the ward and the outside humidity; but I do not recall the detailed results.

DR. HESS (closing): Answering Dr. Gerstenberger, I will repeat what I said before.

While many of the infants showed minor degrees of rickets, only a few of them developed marked rickets. Cod liver oil is started between the second and third week. The quartz lamp has been used for about two years.

Replying to Dr. Sisson's question, I simply mentioned the fact that forty-six of the autopsies showed some degree of atelectasis and many of them showed an open duct and open foramen ovale, but neither the atelectasis nor the patent fetal orifices were considered as causes of death in any of the cases unless they might have been considered as complicating factors when there was other definite pathologic change. I made the statement that the infants having pneumonia died late. Most of them died after the second week, and in those in which atelectasis was still present, I believe it might have been a real factor.

In the group of infants reported as showing atelectasis the pathologic department was responsible for the diagnosis.

As far as the artificial feeding is concerned, I have a decided feeling that breast milk should be given whenever possible. As to the use of lactic acid milk, I have found this to be true: In a considerable number of the cases of diarrhea, I have been in the habit of adding skimmed lactic acid milk to the breast milk, and I believe this is to be a valuable form of corrective dietetic therapy.

DISPLACEMENT OF THE HEART IN PNEUMONIA. DR. J. P. CROZER GRIFFITH.

In almost all of forty cases of apparent pneumonia of one side in which the examination was made by the roentgen ray, the clinical diagnosis was croupous pneumonia. A few of these diagnoses were later discarded on account of development of involvement of both lungs or of empyema, or for other reasons. Sixteen cases showed displacement of the heart to the pneumonic side. Seven of these were reported by way of illustration, with reproduction of the roentgenograms in four cases. Practically nothing on the subject was found in medical literature, with the exception of two contributions by Thoenes and by Wallgren, respectively, the observations of which were largely the same as in the cases now reported. The publications of these authors were discussed. The conclusions drawn are that displacement of the heart in pneumonia is of comparatively frequent occurrence. It is of a temporary nature, often disappearing after the consolidation of the lung has cleared up and sometimes before this has occurred. The cause of the condition was considered. Thoenes regards it as largely due to atelectasis. Wallgren deemed it dependent on compensatory dilatation of the healthy lung, with consequent pushing over of the heart to the affected side. As cases showing the clinical evidences of atelectasis were carefully excluded from the author's list, the conclusions drawn are that the dilatation of the healthy lung is the major cause, although any development of atelectatic patches in the pneumonic lung would aid in producing the cardiac displacement.

The matter appears to be of importance, first, because so little has been written regarding it; second, because the relative frequency with which the displacement occurred in the author's cases shows that the condition is probably

not at all infrequent; and third, because it has a distinct bearing on the diagnosis of massive collapse of the lung. There should be, as a rule, no difficulty in the diagnosis of this disorder, but as the displacement in pneumonia is often considerable, the mere finding of such a condition does not justify the diagnosis of collapse, unless the history and the clinical symptoms and signs are in support of it. The statement which has been made is undoubtedly true, that many cases which have been diagnosed pneumonia were probably instances of collapse, but the converse is equally possible.

DISCUSSION

Dr. John A. Foote, Washington, D. C.: I noticed in the first of the roentgenograms shown by Dr. Griffith that the chest of the infant was pronouncedly rachitic. It is a matter of common observation that infants, especially those of the negro race, who are suffering from advanced rickets, frequently show roentgenographic evidence of unilateral, and sometimes bilateral, atelectatic areas in the lungs. A fairly large number of these have been seen in this clinic, occurring not only in the case of bronchopneumonia, but also in tuberculous infants and even in those suffering from simple bronchitis. In a few infants showing considerable involvement of lung tissue, usually of the bilateral type, some slight degree of displacement of the heart was reported by the roentgenographer. It is interesting to find that the tentative observations in the extremely rachitic child, whose diaphragmatic strength is weakened by the presence of a flexible, rather than a fixed, point in the ribs, are in line with these well authenticated observations of Dr. Griffith in infants suffering from lobar pneumonia.

Dr. Griffith (closing): The question of the influence of atelectasis was, of course, carefully considered, and it was on that account that in every case possible the second roentgenogram was taken, because the question might arise whether the condition was one that existed both before and after the pneumonia. Consequently, as much dependence as possible was placed on the two pictures which showed that the heart after the attack had really moved over from the pneumonic position to the normal one.

The Early Occurrence of Gastric Hemorrhage in Children with Splenomegaly. Dr. Richard M. Smith and Dr. Philip J. Howard.

Severe gastric bleeding in children is relatively uncommon. The sudden onset of severe hematemesis in a child previously well is rare. This may be due to the causes operative in adults, but it is frequently a symptom of splenic anemia, Banti's disease or thrombophlebitis of the splenic and portal veins. Five cases of severe bleeding in young children are reported and are believed to be due to the latter condition. Similar cases in the literature are reviewed.

The symptoms common to all of these cases are as follows: A child previously well and whose history contains no condition which attracted unusual attention suddenly vomits a large amount of bright and clotted blood. This sort of hemorrhage may be so severe as to require immediate transfusion or in some cases to prove fatal. On examination immediately following the hemorrhage these children do not present any evidence of disease except a secondary anemia. If the examination is made somewhat later or before another hemorrhage takes place, there is marked enlargement of the spleen. Repeated hemorrhages at longer or shorter intervals may occur, from any one of which death may result. The hemorrhages may cease spontaneously and the child may

apparently entirely recover. The spleen, however, remains large. The secondary anemia disappears. The striking things about these children are the early appearance of hemorrhage without previous symptoms of illness, the absence of any marked leukopenia, the variation in the size of the spleen after hemorrhage, and the long course of the disease without the development of changes in the liver or any considerable ascites.

Wallgren discusses this condition in a recent monograph. He believes that the enlarged spleen is caused by obstruction to the splenic vein, which result in chronic passive congestion. To compensate for this, the veins of the stomach enlarge and a collateral circulation is established in adhesions which form between the spleen and the diaphragm or the stomach. Rupture of the dilated gastric or esophageal vessels is responsible for the hemorrhage. This explanation seems satisfactory. It is consistent with the examination at autopsy in the fatal cases.

This condition differs in some respects from Banti's disease or splenic anemia, which also is associated with splenic venous obstruction. The question is raised whether this group of cases is sufficiently distinct in its clinical picture to warrant being considered a distinct entity.

Splenectomy is recommended as a means of controlling further hemorrhage and probably of effecting a cure of the disease.

DISCUSSION

Dr. Helmholz: I should like to report a case that is similar to those in the series reported by Dr. Smith, because the spleen was removed but the hemorhages continued. In spite of transfusion, after a period of about nine months this child had severe hemorrhages so that at one time the hemoglobin was down to 10 per cent and the red blood cell count below 1,000,000. The surgeon was finally persuaded to perform an exploratory operation, which revealed an interesting condition. The stomach was opened near the pyloric end, and nothing abnormal was found. There was, however, a peculiar hemorrhagic area in the duodenum. Enlarged vessels were also present about the duodenum. Several of these were tied, and the child made an uneventful recovery and for two years has been free from further hemorrhage.

Dr. F. F. Tisdall, Toronto: The question comes up as to thrombocytopenic purpura. I have had a number of those cases in the last few years in which the patients made a remarkable recovery as soon as the spleen was removed. I would like to ask whether Dr. Smith examined the platelets, or noted the presence of clot-retraction in order to rule out the presence of this disease?

Dr. Abt: No mention was made of Gaucher's disease. In the recent literature, there has been considerable mention of another form of splenomegaly, the so-called Niemann's disease, in which a large lipoid containing cell is found in the spleen, in the thymus and in the mucosa and submucosa of the intestines. In contradistinction to Gaucher's disease, the characteristic cells in Niemann's disease stain positively for the complex lipoids. Gaucher's disease starts early in life and extends over a long period of years, while Niemann's disease affects infants and runs a fatal course in a year or two.

Dr. Smith (closing): A blood count was made in all of the cases, and the spleens were examined carefully for any evidence of specific disease. The detailed accounts of microscopic and macroscopic reports are contained in my paper. The spleens were normal except for the characteristics that I mentioned, signs of chronic congestion.

Second Session, Friday Morning, May 13

The meeting was called to order at 9:45 a. m. by the President.

EVIDENCE OF RICKETS PRIOR TO 1650. DR. JOHN A. FOOTE.

The influence of imbalanced diet and lack of sunshine in the production of rickets is now generally accepted. The theory of an hereditary cause has not been proved, although recent experimental work suggests that improper hygiene and diet in the mother may not actually produce the disease but may result in a resistant type of the malady once the child acquires it. Historically, rickets has followed wars and disease. It is notably present in the populations of crowded industrial cities.

Since the social and climatic conditions that serve to produce this disease are not peculiar to modern times, it would seem reasonable to assume that rickets could always have existed. Contrary to the statements that the bones of Inca children show no evidence of this malady, a rachitic skull from an ancient Peruvian cemetery may be seen in the Army Medical Museum in Washington. A curved radius in an older youth from a prehistoric Indian burial ground in Kentucky in this collection is also believed to be rachitic. Dr. A. Hrdlicka, an authority on physical anthropology, has charge of this collection. Swaddling, a practice among all ancient peoples except the Egyptians and Spartan Greeks, was used to prevent the onset of rickets. Soranus' writings bear testimony to this.

It would be natural to look for evidence of rickets in religious paintings made at the end of the fifteenth century in the growing industrial cities of Germany and the Netherlands, since here could be found the climatic and economic conditions that have inevitably produced the disease in children in the present day. Here also one can find the predisposing effect of war on the civilian population. A school of religious art arose and flourished in both Germany and the Netherlands in the last half of the fifteenth century in which children were used freely as models; this is unusually fortunate for the purpose of this study. An investigation of the works of these artists reveals many pictures of clinical rickets — square heads, pot-bellies, Harrison's groove, and even deformities of the long bones.

Among the artists whose paintings unconsciously represented rickets between 1447 and 1500 are the following: 1447, Stephen Lochner, "Virgin in the Grove of Roses," in the Cologne-Richartz Museum; 1460, Master, the "Life of Mary" and "Adoration of the Child," Cologne-Richartz Museum; 1470, Swabian Master (of Augsburg) "Adoration of the Child," in Augsburg Church of St. Moritz, also "The Nativity" and the "Adoration of the Magi" in the Maximilian Museum. A number of his other pictures show children with stigmas of rickets. 1485, Benhard Strigel of Nuremberg, "The Holy Family," in the Germanic Museum, Nuremberg; 1490, Michael Packer of Nuremberg, "Birth of Christ," St. Wolfgang Church; 1479, Michael Wohlgemut of Nuremberg, "Birth of Christ," Zwickau, Marien Kirche; 1500, Albrecht Durer, Nuremberg, "Madonna with the Siskin." In this painting, the infant holds a flower-ball in his hand.

Among the Netherland painters one finds Bruges Master, 1440 "Adoration of the Magi," Bruges Museum; 1440, Rogier Van Der Weyden, Brussels, "St. Luke Painting the Madonna," Alte Pinakotheck, Munich; 1490, Dirk Bouts Harlem, "Virgin and Child," National Gallery, London. The last shows a splendid clinical picture of Harrison's groove.

The evidence of these artists, who painted what they saw, seems undisputable. There is now no reason, in view of what is known of its causes, to say that rickets is, or must be, a disease exclusively of even remotely modern

times, or that it is a disease called into existence by the peculiar conditions of life in modern civilized communities. Rickets undoubtedly existed to some extent at all times and periods of the world's history, and in many countries evidence found in painting suggests that it was a rather common condition in the industrial cities of Germany and Holland at least 200 years before its description by Glisson, and such evidence is confirmatory of the present day theories of its etiology and pathogenesis.

AN OBSERVATION MADE DURING THE CLINICAL STUDY OF RICKETS IN THE BREAST FED. DR. L. R. DEBUYS (read by title).

THE RELATION OF CRANIOTABES IN PREMATURE INFANTS TO RICKETS. DR. WARREN R. SISSON and ROBERT N. GANZ (by invitation).

The question has been raised as to the nature of the cranial bones in premature infants. This has been commonly regarded as a sign of rickets to which premature infants have been most susceptible. Some observers have questioned the rachitic nature of craniotabes, and evidence is still inadequate to establish the exact pathologic change of the condition.

It is now regarded that a diagnosis of rickets may be based on the calcium and inorganic phosphorus concentration of the blood serum together with roentgenologic observations. Such studies were made on a group of twenty-six premature infants, 80 per cent of whom showed advanced craniotabes. The observations were made over a period of about nine months, from September to May. The diet consisted chiefly of mother's milk, with modifications of boiled milk at intervals. Cod liver oil and orange juice were added to the diet in some instances. The average gain in weight of the infants that developed craniotabes was 0.65 of an ounce daily and that of those who failed to develop craniotabes was 0.26.

Determinations were first made on sixteen premature infants prior to the date of expected birth. In this group, the average calcium concentration was 10.15 mg. per hundred cubic centimeters of blood serum and the average phosphorus concentration was 5.8, giving a calcium phosphorus product of 58.87.

In this group of infants, six failed to develop craniotabes, and these showed an average calcium concentration of 10.36 and an average phosphorus concentration of 5.54 with an average product of 57.4. Repeated roentgenograms taken during this period showed no evidence of rickets.

Similar studies were made on fifteen premature infants during a period of extreme craniotabes, generally from the second to the fifth month. The average calcium concentration of the blood serum of these infants was 10.2 and the average inorganic phosphorus was 6.1, with a product of 63.22. The roentgen-ray studies of this group showed evidence of rickets in one instance.

These results indicate that the calcium and phosphorus concentration of the blood serum of premature infants, prior to expected birth and during the period of active advanced craniotabes, is normal, with a tendency for the calcium to be a low normal and the phosphorus to be slightly above normal.

Craniotabes in prematurely born infants, therefore, does not show the chemical changes in the blood or the roentgenologic observations usually associated with acute rickets. It suggests that the condition is due to an insufficient calcium intake during a period of rapid growth.

THE ANTIRACHITIC EFFECT OF SKYLIGHT. DR. F. F. TISDALL.

The results here reported are some of those obtained in an experiment being conducted in an attempt to determine the variations in the antirachitic effect of sunlight and "skylight" throughout the year. Each week a series of rats aged from 25 to 27 days, were placed on McCollum's rickets producing diet 3143. Some of the rats were placed outside daily from 11 a. m. to 1 p. m. on the sunny side of the laboratory roof, thus receiving both the direct rays from the sun when available, and the reflected rays from the sky (skylight). Others were exposed for the same period on the shady side of the roof, thus receiving only skylight. Control rats were kept inside on the same diet in a room with subdued light. Further control rats were placed on a normal diet. After four weeks the rats were killed by bleeding from the carotid artery under light ether anesthesia. Roentgenograms were taken of the rats. The inorganic phosphate content of the blood and the ash content of the bones were determined. Some of the results are given in the accompanying table. The roentgenograms (a number were shown on lantern slides) show a definite antirachitic effect of skylight even during the winter months.

Antirachitic Effect of Skylight on Rats

	Rachitic Diet, Inorganic Phosphorus per 100 Cc. Blood			Rachitic Diet, per Cent Ash in Bone			Normal Diet, Sunlight 11 to 1 Daily	
For Four Weeks Ending (1927)	Inside Cage, Mg.	Skylight, 11 to 1 Daily, Mg.	Sunlight, 11 to 1 Daily, Mg.	Inside Cage	Skylight, 11 to 1 Daily	Sunlight, 11 to 1 Daily	Inorganic Phosphorus in Blood	Per Cent Ash in Bone
January 3...	1.2	2.4	2.9	30.3	40.5	43.7	6.5	56.7
February 28.	1.4	2.7	4.5	32.0	44.6	51.0	6.3	55.9
March 28....	1.2	2.7	5.2	33.4	46.2	50.4	...	....
April 11.....	...	3.6	7.2	....	51.3	46.7	6.7	58.4
April 18.....	1.6	...	5.1	33.8	....	54.4	...	....
April 25.....	1.4	4.0	...	34.8	50.0	50.5	...	....

CONCLUSIONS

Skylight, which is the reflected light from the sun, produces an antirachitic effect roughly from one half to two thirds of that produced by the available sunlight, which includes the reflected light from the sky. The practical application of this work is that infants may be placed outdoors but protected from the direct sun and still receive a great antirachitic effect from the reflected ultraviolet rays of the sky.

NOTE.—Dr. C. H. Best of the Department of Physiological Hygiene, University of Toronto, measured the ultraviolet content of skylight alone. He also measured the ultraviolet content of the available sunlight, which includes the reflected light from the sky. These measurements were made by means of Leonard Hill's methylene blue solution. During the last week in April and the first week in May, he found that the ultraviolet content of skylight alone was about 60 per cent of the ultraviolet content of sunlight.

OBSERVATIONS ON RACHITIC SPASMOPHILIA AND "LOW CALCIUM" RICKETS. DR. HENRY J. GERSTENBERGER, DR. J. I. HARTMAN (by invitation), DR. T. S. WILDER (by invitation) and DR. D. S. SMITH (by invitation).

The report is based on prolonged observations made on fifty-eight hospitalized cases of rickets, forty-nine of which showed symptoms of spasmophilia and nine of which did not.

(1) Pure cases of primary active non-healing human rickets are characterized by a low inorganic phosphate content of the blood serum and when adequately and continuously treated proceed to complete healing without the development of spasmophilic symptoms.

(2) Spasmophilia as it is ordinarily encountered in human infants develops in rachitic subjects who in the great majority of the cases give evidence of bone healing having occurred to a certain degree, which healing only can have been the result of the action of some antirachitic agent administered in a peculiar way either intentionally or accidentally.

(3) It is suggested that the term "rachitic spasmophilia" be used in order to designate its dependence for its development on the preliminary presence of rickets.

(4) Rachitic spasmophilia is characterized usually by a low calcium and a high inorganic phosphate content of the blood serum and is a form of rickets which has experienced a peculiar type of healing, as the result of the action in some manner of interrupted treatment.

(5) The variation in incidence of rachitic spasmophilia, we believe, is usually due to conditions that cause interruption of exposure to sunlight.

In the spring, the increase in sunshine gives the opportunity for increased but interrupted healing of winter rickets, and in the fall the decrease in sunshine only gives opportunity for inadequate and interrupted exposure of the mild cases of rickets which are found mainly in young infants who because of their age have been protected against sunlight and who have grown rapidly.

(6) The term low calcium rickets should not be used in connection with human rickets as it is with the rickets of rats, because whenever a decidedly reduced calcium level is found in the blood serum of human infants, a low phosphorus rickets has preceded its appearance and has in some manner been subjected to interrupted influence of the antirachitic factor.

(7) A low calcium-low phosphorus rickets develops in human infants when a low phosphorus rickets has proceeded, usually sooner or later accompanied by spasmophilic symptoms, to a stage of peculiar healing and when the low phosphorus rickets is followed by a development of rickets. In these cases spasmophilic symptoms may persist even though the phosphorus level be lowered, if the calcium level, as is often the case, is very low when the second rickets is developing.

(8) A single exposure of a low phosphorus rickets to ultraviolet rays caused the development of healing which continued for sixty-one days and which was accompanied toward the end by the development of spasmophilic symptoms (low cathodal opening contraction and low blood serum calcium).

DISCUSSION

Dr. F. W. Schlutz, Minneapolis, Minn.: The observation of Dr. Tisdall in regard to the effect of skylight is interesting indeed. Most of you will recall the remarks of Dr. Findlay a few years ago, in giving a report of his experiments with dogs. I remember he made the point that dogs did not develop rickets even if kept from the sunlight. It is known from clinical observation that the rachitic infant will improve if not exposed to the sun directly but if put in the open air. Sunlight does aid more than any other factor, with the exception, probably, of cod liver oil. The effect of skylight probably explains the results that Dr. Findlay got at that time.

DR. BLACKFAN: It is interesting in connection with Dr. Tisdall's studies to speak of some studies that have been made by Dr. Wyman in Boston. He studied the effects on rats of ultraviolet rays through Corning glass, quartz glass and vitaglass, and his results are comparable to those which Dr. Tisdall has reported. In addition, last winter he exposed infants with active rickets to the sunlight penetrating through quartz glass, and this year he has exposed infants to the rays penetrating through quartz glass, Corning glass and vitaglass. As determined by the rise in calcium and phosphorus products, and confirmed by the roentgen-ray, these children have responded much better to the rays penetrating through quartz glass and Corning glass than to the rays penetrating through the cathedral form of glass.

DR. ALFRED HAND, Philadelphia: Dr. Foote referred to the belief formerly prevalent that rickets was hereditary, and it is easy to see a reason for that idea, since so many of the adults, as well as the infants, in the pictures of medieval art which have been shown by Dr. Foote, bear evidences of having been rachitic.

I wish to thank Dr. Tisdall for his demonstration of the antirachitic value of skylight, for in recent years it has been necessary for me to tell some of my co-workers, as I pull back some of the beds on the roof into the shade, that there is such a thing as sunstroke on hot summer days in Philadelphia, for I have seen it. I am therefore glad to know that, while saving some lives, I am not depriving the patients of all antirachitic benefit.

DR. J. H. MASON KNOX, Baltimore: I should like to ask a question from a practical point of view. Have you experience in the treatment of infants and children as to the temperature at which it is safe to expose them to skylight; also what glass medium do you find that best transmits the violet rays? If skylight has such antirachitic effect, its use would be particularly practical in summer weather, when there is real danger of burning the skin of children, especially of infants.

DR. B. K. HAMILTON, Brookline, Mass.: I was extremely interested in Dr. Sisson's paper because it shows that here we have a condition which gives typical symptoms of rickets but which still has a normal blood chemistry. I wonder if the time will come when one will have to decide whether rickets is a clinical or an etiologic entity.

I wanted to ask one question. Dr. Sisson has observed these infants during the first months of life. I should like to ask if he has followed these premature infants for four, five or six months, for that is the age when infants born at full term get rickets in the long bones and whether these premature infants then showed symptoms of rickets in the long bones?

DR. HEIMAN: In reference to the study of craniotabes, I should like to call attention to another condition that simulates craniotabes clinically, and that is the so-called osteoporosis. I recall two cases. I saw one at a later age when I could almost exclude rickets, when there was a distinctive maldevelopment in the flat bones. The other child was brought to my office only about a month ago with a similar condition. I believe that one can almost differentiate those cases clinically from the true craniotabes that appears early in childhood, but I think that one should take this other condition into consideration when one sees these cases and studies them from a physiologic standpoint.

DR. H. J. GERSTENBERGER, Cleveland: I should like to ask Dr. Sisson how long the infant that did not develop rickets was under observation, and whether

the determinations of calcium and phosphorus had been made at frequent intervals? I have found that unless they are made at least every four weeks one may miss the changes. Sometimes one even may get an abnormal calcium or phosphorus figure within less than four weeks. If the determinations made are too far apart, changes that occurred will be missed. Because normal figures only are found does not, I think, prove that rickets has not been present.

DR. SISSON (closing): Replying to Dr. Hamilton's question, we have made only two determinations of calcium and phosphorus in these infants at the age of 5 to 7 months. Both of the cases previously studied showed normal characteristics. We have, however, made eighteen studies by roentgen-ray examination of the bones that had been previously studied, and all of those showed essentially normal changes. Three, however, showed signs of slightly healed rickets. I think there were about 80 per cent normal, and the others were healed or improved. I do not think that I can answer Dr. Gerstenberger's question because I have not the figures here. The determinations were taken theoretically every four weeks. The patient he referred to was observed for seven or eight months, and I think there were periods over six or eight weeks or longer during which calcium determinations were not made.

DR. TISDALL (closing): Dr. Schlutz asked about fresh air alone. We controlled the question of fresh air by putting the rats outdoors and protecting them from any light. Those rats developed rickets of the same degree as those that were kept inside. That is, fresh air alone without the light has no antirachitic effect.

Dr. Knox asked about the temperature. These experiments were done with rats, which are fur bearing animals, and we cannot say what we would do with human beings.

We found that there was a tremendous increase in the antirachitic effect with both sunlight and skylight in the last week of February. That is the time of year that the sun begins to melt the snow. At that time, it took a tremendous jump in one week's time. During December, January and the first part of February, the antirachitic effect of light which had gone through the glass was practically negligible; it was practically of no value. However, the value of it at the present time is definite, that is, since the end of February and March. If it is too cold to expose the infants outside without some protection, the vitaglass is of definite value. Experiments with the other glasses have not gone far enough for any conclusions to be drawn.

A STUDY OF ALIMENTARY "PROTEIN FEVER." DR. L. A. HOAG, HELEN RIVKIN (by invitation), DR. S. Z. LEVINE (by invitation), DR. J. R. WILSON (by invitation), FRIEDA BERLINER (by invitation), DR. CARL WEIGELE (by invitation) and DR. A. F. ANDERSON (by invitation).

Fever, without other symptoms except thirst, restlessness and dry skin, was produced in twenty infants by the administration of diets containing a proper concentration of either "Casec" (ash, 4.5 per cent), or "Casein-Harris" (ash, 0.6 per cent), purified egg-white protein, urea, or sodium chloride. All the symptoms were relieved promptly by giving large doses of water by mouth. Hypodermoclyses of water were less effective, and physiologic sodium saline solution given either by mouth or under the skin was almost totally ineffective in reducing the fever. The fluid treatments that were successful produced profuse perspiration. The defervescence of the fever need not be preceded by

or accompanied by a lowering in the concentration of blood nonprotein nitrogen. Urinary organic acids were not increased by urea or sodium chloride.

Data from the studies of the respiratory metabolism showed that the "specific dynamic action" of a high protein diet did not cause fever when accompanied by sufficient water. They also confirmed the fact that urea has no "specific dynamic action" and emphasized the importance of vaporization of water in dissipating heat during defervescence of these fevers.

Attempts to demonstrate antigen in the serum at the height of "protein fever" were unsuccessful in the eight patients examined.

The observations all suggest the possibility that end-products of the ingested pyretogens, whether they are stored in the tissues or excreted by the kidneys, bind osmotically more water than is received in the fever-producing diets. The depletion of the body reserve of water through attempts to remedy this deficiency curtails the amount available for vaporization and thus interferes with heat dissipation to such an extent that fever develops.

DISCUSSION

DR. TALBOT: I might add that one factor which I think substantiates Dr. Hoag's theory that the water reserve is drawn from the tissues and possibly cannot be useful in the evaporation of heat is that with the increase in fever, there is an increase in the basal metabolism; we have recently shown that there is also a corresponding increase in the insensible perspiration, so that if there is an increase there is the possibility that there is less water available for evaporation from the surface of the body. The body itself in the few cases of fever that I have had the opportunity to study tends to conserve its fluid by reducing the urinary output to a marked extent. In one instance, it was so reduced in salt fever that for a period of six hours no urine at all was passed, and the body during that time so adjusted itself that when it was ready without the addition of fluid the same sequence of events happened that Dr. Hoag has described. The skin changed from a color that simulated scarlet fever; the child started to perspire profusely, and cooling resulted with a return to the normal appearance of the skin in a short time.

DR. CLIFFORD G. GRULEE, Chicago: Clinically, there is one condition which of course parallels protein fever, and that is the fever that results when concentrated food is fed in cases of pylorospasm. If water is added after a prolonged period of feeding of concentrated carbohydrate foods, to these infants having pylorospasm they will go into a state of collapse: I saw one child that nearly died as a result of being given a large amount of water following a prolonged period of cereal feeding. If the water is added gradually or the thickness of the food gradually decreased, a gradual decline in the temperature will result. It seems from what Dr. Hoag has said that there is a certain parallelism between the protein fever studied by him and the fever that results from concentrated food in pylorospasm.

One point I should like to make is that it has been said that in the concentrated cereal feedings the fever is due to the protein element in the food which is, of course, always present to a large degree. There is, it seems, some question about this since one can produce a like fever with casein.

DR. BELA SCHICK, New York: Dr. Hoag spoke of giving water by mouth and by subcutaneous injection in order to lower the temperature. I would like to ask him what is the effect of cold application on the skin (sponging, etc.)?

DR. HOAG (closing): Answering Dr. Schick's question, up to the present time we have not made any observations on reduction of the fever except by the administration of fluids by mouth or under the skin.

The fever which accompanies the administration of salts to the point of complete anuria may be theoretically explained by saying that water may be just as effectively lost from the point of view of vaporization, by being held in the tissues, as by excretion through the kidneys.

We point out finally that, in agreement with the observation that concentration of all the different food types under certain extreme conditions may lead to fever, apparently the relation between the total amount of excretory substances in the diet and the amount of fluid that is available to assist in storage or excretion determines whether or not the water reserve of the body will be drawn on sufficiently to interfere with loss of heat.

CHVOSTEK'S FACIALIS SIGN IN NEW-BORN INFANTS. DR. FRANK E. STEVENSON (by invitation), DR. A. GRAEME MITCHELL and DR. CARL A. KOCH (by invitation).

In cases of tetany, Chvostek called attention to a sudden tic-like contraction of certain muscles supplied by the facial nerve, which was elicited by tapping over the middle of the cheek. Later similar phenomena such as Schultz's sign, Deiss' sign, Lust's sign, Trousseau's sign and the femoralis reflex have been pointed out as being of diagnostic value in tetany. All of these signs vary in the frequency with which they are found in tetany as well as in their diagnostic value. Probably not one of them can be accepted alone as being unquestionably pathognomonic of tetany. Various theories have been advanced in explanation of the mechanism of these phenomena. It has been thought that the hyperirritability may be localized in the muscle itself, that a spinal reflex is involved and that there is spasm of the blood vessels of the nerves. The consensus of opinion, however, is that it is the nerve trunk itself which is hypersensitive as a consequence of the lowered amount of calcium present.

Our examinations were made on new-born infants. A total of fifty-five were studied, varying in age from 12 hours to 21 days. Blood calcium determinations were made on all the infants and electrical examinations on some of them.

The conclusions derived from this study were as follows:

1. It was found that the Chvostek sign occurred consistently in normal new-born infants.

2. It was always possible to elicit the sign in sleeping infants, but when the patient was awake, even though quiet, the reaction was frequently negative. In crying or restless infants, the sign was never obtained.

3. Blood calcium determinations were within normal limits in the majority of the infants; in the others they were normal, with one exception; the amount of blood calcium was above the limit at which tetany usually occurs.

4. Electrical reactions were obtained on fifteen infants, and in all instances these were normal.

5. As Chvostek's facialis phenomenon is found in new-born infants without clinical, serologic or electrical evidences of tetany, it cannot be regarded as a pathognomonic symptom of this condition in early infancy.

DISCUSSION

DR. GERSTENBERGER: I should like to ask if any of the cases showed a severe facial phenomenon? As I understand it, they were mild. I had an

opportunity to register a positive Chvostek's sign in two infants who were about 3 weeks old and both of whom had hemorrhage of the brain. It is known that if a hemorhage is present in the lateral ventricles, trismus is liable to occur.

I should like to know also if any of the infants who had hemorrhage of the brain and who came to autopsy showed a severe facial phenomenon when alive?

DR. MITCHELL: We excluded all infants except those who were normal. In the study we included only those infants who had no sign of injury of the brain or any other abnormal symptom. The sign was very definite, as it would be obtained in any older child with tetany but, as I stated, it was only in 11 per cent of this particular group that we obtained it all over the side of the cheek — that is, the corner of the eye, and the nose and the mouth. In about one third of the cases, it was obtained only about the mouth.

(To be continued)

Book Reviews

KINDERPFLEGE. By PROF. DR. E. NOBEL and PROF. DR. C. PIRQUET. Price, 3 marks. Paper. Pp. 104. Vienna: Julius Springer, 1927.

In response to popular demand, the authors have selected from the subject matter of their textbook, "Kinderheilkunde für Schwestern und Fürsorgerinnen," the portions that deal with the care of the normal infant. The material has been rewritten and is intended for the use of mothers and nurses.

Following a brief review of the chemistry and physiology of nutrition in early life, the "Nem" system of infant feeding devised by Pirquet is described in detail. Elaborate tables are given which are designed to aid in the preparation, measuring and serving of foodstuffs in accordance with this method.

Under the subject of breast-milk feeding, the authors do not interdict the mother's eating spicy or highly seasoned foods if she likes them. They recommend the three hour nursing or bottle interval, and six feedings a day.

The formula most commonly employed contains equal parts of boiled or pasteurized milk and a 17 per cent cane sugar solution. Premature infants are, in some cases, fed with human milk enriched with 8.5 per cent sugar. Eiweiss milk is described. No mention is made of other forms of lactic acid milk. Infants are given cereals and vegetables at an early age.

The concluding chapters are devoted to detailed directions in the daily care of infants. There is no discussion of treatment. A few warning symptoms are given, with the advice that the infant be taken to the physician at once. The book should prove valuable to the laity, for whom it is intended. To the American physician, it is interesting as a comparison with European methods of feeding and caring for infants.

SHOULD WE BE VACCINATED? By BERNARD J. STERN. Pp. 146. Price, $1.50. New York: Harper and Brothers, 1927.

To those who have accepted unquestioningly the value of vaccination, this exposition of the battles that have been waged for and against it is enlightening. From a medical point of view, it is interesting to note that Jenner and his colleagues at first claimed lasting immunity from a single vaccination, and even in the face of proof to the contrary many of them refused to modify their original claims. From a sociologic standpoint, the statutes compelling vaccination have roused the ever ready cry of "interference with individual liberty." It was in connection with the vaccination controversy that Dr. James Gregory first remarked, "England is a free country and the freedom which every Englishman chiefly values is the freedom of doing what is foolish and wrong and going to the devil in his own way."

AN AUTOBIOGRAPHY. By LEDYARD W. SARGENT, Edited by R. Tait McKenzie. Price, $2. Pp. 221. Philadelphia: Lea & Febiger, 1927.

Unclouded by a review of old controversies in which Sargent participated, this narrative has about it much of an informal conversational style. After detailing the pleasures of a boyhood spent by the sea and a trial of life before the mast, he tells of the adventures as a circus performer, of his first attempts at physical education at Yale, of the final establishment of physical education in the curriculum at Harvard and of the development of the Summer School of Physical Education.

Between the lines one may read of the influence on Sargent of the men whose books he read—Darwin, Spencer and Cutter.

Directory of Pediatric Societies

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Secretary: Dr. C. A. Aldrich, 545 Lincoln Ave., Winnetka, Ill.
Place: Minneapolis. Time: To be decided later.

AMERICAN PEDIATRIC SOCIETY

President: Dr. J. Claxton Gittings, 1828 Pine St., Philadelphia.
Secretary: Dr. Howard Childs Carpenter, 1805 Spruce St., Philadelphia.
Place: Washington, D. C. Time: April 30 to May 2, 1928.

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AMERICAN CHILD HEALTH ASSOCIATION

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Secretary: Dr. H. T. Price, 121 University Place, Pittsburgh.
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President: Dr. Robert A. Strong, Pass Christian, Miss.
Secretary: Dr. Hugh L. Dwyer, Medical Arts Bldg., Kansas City, Mo.
Place: Memphis, Tenn. Time: Nov. 14 to 17, 1927.

LOCAL

PEDIATRIC SECTION OF FULTON COUNTY MEDICAL SOCIETY, ATLANTA, GA.

President: Dr. William W. Anderson, 362 Peachtree St., Atlanta.
Secretary: Dr. Lee Bivings, Exchange Pl., Atlanta.
Place: Academy of Medicine, 32 Howard St., Atlanta.
Time: Second Thursday of each month from September to April, at 8 p. m.

BROOKLYN PEDIATRIC SOCIETY

President: Dr Harold L. Barnes, 1235 Dean St., Brooklyn.
Secretary: Dr. Charles A. Weymuller, 96 Joralemon St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Last Wednesday of each month, except June, July and August.

CHICAGO PEDIATRIC SOCIETY

President: Dr. George Baxter, 4603 Broadway, Chicago.
Secretary: Dr. J. K. Calvin, 104 S. Michigan Ave., Chicago.
Place: City Club. Time: Third Tuesday of each month.

THE PEDIATRIC SECTION OF THE ACADEMY OF MEDICINE OF CLEVELAND

Chairman: Dr. Henry J. Gerstenberger, 2103 Adelbert Road, Cleveland.
Secretary: Dr. Charles W. Burhans, Lakeside Hospital, Cleveland.
Place: 2009 Adelbert Road. Time: Feb. 10, May 7, Sept. 22 and Dec. 15.

DETROIT PEDIATRIC SOCIETY

President: Dr. Thomas B. Cooley, 987 Jefferson Avenue, East, Detroit.
Secretary: Dr. W. S. O'Donnell, 1563 David Whitney Bldg., Detroit.
Place: Children's Hospital of Michigan. Time: No fixed date; approximately once a month.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. L. R. De Buys, 1487 Delachaise St., New Orleans.
Secretary: Dr. F. J. Kinberger, 3601 Prytania St., New Orleans.
Place: New Orleans. Time: April 25, 1927.

MEMPHIS PEDIATRIC SOCIETY

President: Dr. Walter L. Rucks, 1074 Madison Ave., Memphis, Tenn.
Secretary: Dr. J. B. Blue, Columbian Mutual Tower, Memphis, Tenn.
Place: Baptist Memorial Hospital. Time: Second Tuesday of each month.

MILWAUKEE PEDIATRIC SOCIETY

President: Dr. Roy M. Greenthal, 141 East Wisconsin Ave., Milwaukee.
Secretary: Dr. M. G. Peterman, 167 Seventeenth St., Milwaukee.
Place: Children's Hospital, Milwaukee. Time: Second Wednesday of each alternate month.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. James Herbert Young, 66 Commonwealth Ave., Boston.
Secretary: Dr. Thomas Lanman, 286 Marlborough St., Boston.
Place: Boston Medical Library. Time: Second Friday of each month.

PEDIATRIC SECTION OF THE NEW YORK ACADEMY OF MEDICINE

Chairman: Dr. Lewis C. Schroeder, 39 E. 61st St., New York.
Secretary: Dr. William R. May, 8 East 66th St., New York.
Place: New York Academy of Medicine. Time: Second Thursday of each month.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. C. F. Gelston, 384 Post St., San Francisco.
Secretary: Dr. Mary H. Layman, 2116 Pacific Ave., San Francisco.
Place: Alternates between Stanford University Hospital, University of California Hospital, and Children's Hospital. Time: Three or four times a season.

NORTHWESTERN PEDIATRIC SOCIETY

President: Dr. C. A. Stewart, 730 La Salle Bldg., Minneapolis.
Secretary: Dr. E. S. Platou, 730 La Salle Bldg., Minneapolis.
Place: Three at the Medical Campus, Minneapolis and one at the Town and County Club. Time: Winter, Spring, Summer, Fall.

PHILADELPHIA PEDIATRIC SOCIETY

President: Dr. Frederick Fraley (Retiring), Overbrook, Pa.
Secretary: Dr. John P. Scott, 2040 Pine St., Philadelphia.
Place: College of Physicians, 19 S. 22nd St., Philadelphia. Time: Second Tuesday of each month.

THE ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. W. Wiley Jones, Majestic Bldg., Denver.
Secretary: Dr. Berryman Green, Republic Bldg., Denver.
Time: Third Saturday of each month, 2 to 4 p. m. Place: Children's Hospital, Denver.

ST. LOUIS PEDIATRIC SOCIETY

President: Dr. T. Wistor White, Lister Bldg., St. Louis.
Secretary: Dr. Edwin Rohlfing, Grand Blvd. and Wyoming St., St. Louis.
Place: St. Louis Children's Hospital. Time: Third Friday in each month.

SOUTHWESTERN PEDIATRIC SOCIETY

President: Dr. Oscar Reiss, 2007 Wilshire Blvd., Los Angeles.
Secretary: Dr. Wm. Sidney Bowers, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

PEDIATRIC SECTION, ACADEMY OF MEDICINE,LTORONTO

President: Dr. M. A. Cox, 34 St. Clair Ave. W., Toronto.
Secretary: Dr. F. R. Hassard, 1361 King St., W., Toronto.
Time: November 17, December 15, February 16 and March 15.

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CONTENTS

PAGE

The Influence of Pathology on the Development of Pediatrics. Isaac A. Abt, M.D., Chicago 1

Respiratory Anaphylaxis: Sensitization, Shock, Bronchial Asthma and Death Induced in the Guinea-Pig by the Nasal Inhalation of Dry Horse Dander. Bret Ratner, M.D.; Holmes C. Jackson, Ph.D., and Helen Lee Gruehl, B.A., New York 23

The Relation of Maternal Diet to Hemorrhage in the New-Born. C. Ulysses Moore, M.D., and Jesse Laird Brodie, M.A., Portland, Ore. 53

Malignant Neuroblastoma: Report of Three Cases. Boris Kwartin, M.D., and J. Russell Twiss, M.D., New York .. 61

Sickle Cell Anemia: Report of a Case with Splenectomy. Walter Blair Stewart, M.D., Atlantic City, N. J. 72

Dermatoses Due to Light Sensitization, with Special Reference to the Cutaneous Dangers of Ultraviolet Radiation in Children. Sigmund S. Greenbaum, M.D., Philadelphia 81

Progress in Pediatrics:

Child Health in the Past. Philip Van Ingen, M.D., New York 95

News and Comment 103

Obituary:

Abraham Zingher, M.D. 105

Abstracts from Current Literature 106

Society Transactions:

Pediatric Section of the Academy of Medicine of Cleveland 131

American Pediatric Society (First and Second Sessions) 133

Book Reviews 154

Directory of Pediatric Societies 155